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SCIENTIFIC OPINION

Scientific Opinion on Dietary Reference Values for magnesium¹

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)^{2,3}

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies (NDA) derived Dietary Reference Values (DRVs) for magnesium. The Panel considers that Average Requirements (ARs) and Population Reference Intakes (PRIs) for magnesium cannot be derived for adults, infants or children, and therefore defines Adequate Intakes (AIs), based on observed intakes in healthy populations in the European Union (EU). This approach considers the range of average magnesium intakes estimated by EFSA from dietary surveys in children and adults in nine EU countries. For adults, an AI for magnesium is set at 350 mg/day for men and 300 mg/day for women. For children aged 1 to < 3 years, an AI for magnesium is set at 170 mg/day for both sexes. For children aged 3 to < 10 years, an AI for magnesium is set at 230 mg/day for both sexes. For children aged 10 to < 18 years, an AI for magnesium is set at 300 mg/day for boys and 250 mg/day for girls. For infants aged 7–11 months, an AI for magnesium of 80 mg/day is derived by extrapolating upwards from the estimated magnesium intake in exclusively breast-fed infants aged 0–6 months and by considering observed average intakes in the few surveys for which data are available. For pregnant and lactating women, the Panel considers that there is no evidence for an increased need for magnesium, and the same AI is set for them as for non-pregnant, non-lactating women.

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KEY WORDS

magnesium, balance, observed intake, Adequate Intake, Dietary Reference Value

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SUMMARY

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a Scientific Opinion on Dietary Reference Values (DRVs) for the European population, including magnesium.

Magnesium is an alkaline earth metal. It occurs as the free cation Mg^{2+} in aqueous solutions or as the mineral part of a large variety of compounds, including chlorides, carbonates and hydroxides. Magnesium is a cofactor of more than 300 enzymatic reactions, acting either on the enzyme itself as a structural or catalytic component or on the substrate, especially for reactions involving ATP, which make magnesium essential in the intermediary metabolism for the synthesis of carbohydrates, lipids, nucleic acids and proteins, as well as for specific actions in various organs in the neuromuscular or cardiovascular system.

Magnesium deficiency can cause hypocalcaemia and hypokalaemia, leading to neurological or cardiac symptoms when it is associated with marked hypomagnesaemia. Owing to the widespread involvement of magnesium in numerous physiological functions and the metabolic interactions between magnesium and other minerals, it is difficult to relate magnesium deficiency to specific symptoms.

Magnesium absorption takes place in the distal intestine, mainly as the ionised form. Percentage absorption is generally considered to be 40–50 %, but figures from 10 to 70 % have also been reported. Magnesium absorption can be inhibited by phytic acid and phosphate and enhanced by the fermentation of soluble dietary fibre, although the physiological relevance of these interactions at adequate intakes remains to be established.

The majority of the body magnesium content is stored in bone (about 60 %) and muscle (about 25 %). A small amount is present in the serum, mainly as the free cation. Most cells are able to actively and rapidly buffer magnesium loss or accumulation through the involvement of specific magnesium transporters. The kidney plays a major role in magnesium homeostasis and maintenance of serum concentration. Urinary magnesium excretion is increased by high natriuresis, osmotic load and metabolic acidosis, and reduced by metabolic alkalosis, parathyroid hormone and, possibly, calcitonin. A large proportion of the magnesium content of faeces stems from unabsorbed magnesium. Endogenous magnesium is lost through bile, pancreatic and intestinal juices, and intestinal cells, and part of this can be reabsorbed. Magnesium losses through sweat are modest and very variable, depending on the techniques used for sweat collection, and losses through menstruation are negligible.

There is some evidence that urinary magnesium concentration reflects magnesium intake. Urinary, faecal, serum and erythrocyte magnesium concentrations have been used for the assessment of magnesium status, with serum magnesium concentration being the most frequently used marker. However, the Panel considers that the usefulness of serum magnesium concentration as a marker of intake or status is questionable and that there are at present no appropriate biomarkers for magnesium status that can be used for deriving DRVs for magnesium.

The Panel notes that a recent pooled analysis of balance studies in adults suggests that zero magnesium balance may occur at a magnesium intake of 165 mg/day. The Panel also notes that results of some large-scale and long-term prospective observational studies point to an inverse relationship between magnesium intake and the risk of diabetes mellitus type 2.

Foods rich in magnesium are nuts, whole grains and grain products, fish and seafood, several vegetables, legumes, berries, banana and some coffee and cocoa beverage preparations. The magnesium content of tap/bottled water can make a significant contribution to intake. On the basis of data from 13 dietary surveys in nine European Union (EU) countries, dietary intake of magnesium was estimated by EFSA using food consumption data from the EFSA Comprehensive European Food Consumption Database and composition data from the EFSA Food Composition Database.

For both sexes combined, average magnesium intake ranged from 72 to 120 mg/day (25–45 mg/MJ, 9.2–12.7 mg/kg body weight per day) in infants (< 1 year of age); from 153 to 188 mg/day (35–45 mg/MJ, 12.7–15.8 mg/kg body weight per day) in children aged 1 to < 3 years; from 184 to 281 mg/day (28–43 mg/MJ, 7.6–13.0 mg/kg body weight per day) in children aged 3 to < 10 years; from 213 to 384 mg/day (28–44 mg/MJ, 4.2–7.7 mg/kg body weight per day) in children aged 10 to < 18 years; and from 232 to 439 mg/day (35–51 mg/MJ, 3.4–5.3 mg/kg body weight per day) in adults (\geq 18 years). The main food groups contributing to magnesium intake were grains and grain-based products, milk and milk products, and coffee, cocoa, tea and infusions.

Considering all the evidence available, i.e. from balance studies and prospective observational studies, the Panel decided to set an Adequate Intake (AI) based on observed intakes in several EU countries. For adults of all ages, the Panel proposed to set AIs according to sex. Considering the distribution of observed average intakes (males 264–439 mg/day; females 232–357 mg/day), the Panel proposed an AI for all adult men over 18 years of 350 mg/day and for all adult women an AI of 300 mg/day, after rounding.

The Panel also decided to set an AI for infants aged 7–11 months and children based on observed intakes in several EU countries. For infants aged 7–11 months, an AI in line with the proposal of the SCF (1993) of 80 mg/day was set. This value represents, after rounding, the midpoint (78 mg/day) of the range between 35 mg/day (magnesium intake estimated by extrapolation using isometric scaling from intakes in breast-fed infants aged 0–6 months) and 120 mg/day (highest value of the range of observed mean intakes in the EU countries for which data are available). For children aged 1 to < 10 years, considering the absence of a strong basis for a distinct value according to sex and the distribution of observed mean intakes, AIs were set at the midpoint of average intakes (170 mg/day for boys and girls aged 1 to < 3 years, and 230 mg/day for boys and girls aged 3 to < 10 years). For children aged 10 to < 18 years, considering the rather large differences in magnesium intakes between boys and girls, the Panel proposed to set AIs according to sex, and to select the midpoints of average intakes as AIs, i.e. 300 mg/day for boys and 250 mg/day for girls.

Considering that pregnancy induces only a small increase in magnesium requirement, which is probably covered by adaptive physiological mechanisms, the Panel considers that the AI for non-pregnant women also applies to pregnant women. For lactating women, considering that 25 mg/day is secreted with breast milk during the first six months of exclusive breastfeeding and that there is the possibility of adaptation of magnesium metabolism, at the level of both absorption and elimination, the Panel considers that the AI for non-pregnant non-lactating women also applies to lactating women.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The scientific advice on nutrient intakes is important as the basis of Community action in the field of nutrition, for example such advice has in the past been used as the basis of nutrition labelling. The Scientific Committee for Food (SCF) report on nutrient and energy intakes for the European Community dates from 1993. There is a need to review and, if necessary, to update these earlier recommendations to ensure that the Community action in the area of nutrition is underpinned by the latest scientific advice.

In 1993, the SCF adopted an opinion on the nutrient and energy intakes for the European Community.⁴ The report provided Reference Intakes for energy, certain macronutrients and micronutrients, but it did not include certain substances of physiological importance, for example dietary fibre.

Since then new scientific data have become available for some of the nutrients, and scientific advisory bodies in many European Union Member States and in the United States have reported on recommended dietary intakes. For a number of nutrients these newly established (national) recommendations differ from the reference intakes in the SCF (1993) report. Although there is considerable consensus between these newly derived (national) recommendations, differing opinions remain on some of the recommendations. Therefore, there is a need to review the existing EU Reference Intakes in the light of new scientific evidence, and taking into account the more recently reported national recommendations. There is also a need to include dietary components that were not covered in the SCF opinion of 1993, such as dietary fibre, and to consider whether it might be appropriate to establish reference intakes for other (essential) substances with a physiological effect.

In this context EFSA is requested to consider the existing Population Reference Intakes for energy, micro- and macronutrients and certain other dietary components, to review and complete the SCF recommendations, in the light of new evidence, and in addition advise on a Population Reference Intake for dietary fibre.

For communication of nutrition and healthy eating messages to the public it is generally more appropriate to express recommendations for the intake of individual nutrients or substances in food-based terms. In this context EFSA is asked to provide assistance on the translation of nutrient based recommendations for a healthy diet into food based recommendations intended for the population as a whole.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 29 (1)(a) and Article 31 of Regulation (EC) No. 178/2002,⁵ the Commission requests EFSA to review the existing advice of the Scientific Committee for Food on population reference intakes for energy, nutrients and other substances with a nutritional or physiological effect in the context of a balanced diet which, when part of an overall healthy lifestyle, contribute to good health through optimal nutrition.

In the first instance EFSA is asked to provide advice on energy, macronutrients and dietary fibre. Specifically advice is requested on the following dietary components:

- Carbohydrates, including sugars;
- Fats, including saturated fatty acids, polyunsaturated fatty acids and monounsaturated fatty acids, *trans* fatty acids;

⁴ Scientific Committee for Food, 1993. Nutrient and energy intakes for the European Community. Reports of the Scientific Committee for Food, 31st series. Food – Science and Technique, European Commission, Luxembourg, 248 pp.

⁵ Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–24.

- Protein;
- Dietary fibre.

Following on from the first part of the task, EFSA is asked to advise on population reference intakes of micronutrients in the diet and, if considered appropriate, other essential substances with a nutritional or physiological effect in the context of a balanced diet which, when part of an overall healthy lifestyle, contribute to good health through optimal nutrition.

Finally, EFSA is asked to provide guidance on the translation of nutrient based dietary advice into guidance, intended for the European population as a whole, on the contribution of different foods or categories of foods to an overall diet that would help to maintain good health through optimal nutrition (food-based dietary guidelines).

ASSESSMENT

1. Introduction

In 1993, the Scientific Committee for Food (SCF, 1993) adopted an opinion on the nutrient and energy intakes for the European Community. For magnesium, the SCF did not set a Population Reference Intake (PRI) but instead set an Acceptable Range of Intakes for adults, including pregnant and lactating women. For children, approximate PRIs were defined on the basis of body weight.

2. Definition/category

2.1. Chemistry

Magnesium (atomic number 12, atomic mass 24.30 Da) is an alkaline earth metal belonging to the third period of the periodic table of the elements. It is the eighth most abundant element in the earth's crust and the eleventh most abundant element in the human body. Like calcium, its oxidation state is +2 and, owing to its strong reactivity, it does not occur in the native metallic state, but rather as the free cation Mg^{2+} in aqueous solution or as the mineral part of a large variety of compounds, including chlorides, carbonates and hydroxides. It can react with nitrogen, phosphorus, sulphur and halides; however, its bond to protein or other biological molecules tends to be weaker than that of calcium (Saris et al., 2000). There are three natural stable isotopes, i.e. ^{24}Mg (natural abundance 79 %), ^{25}Mg (10 %) and ^{26}Mg (11 %).

2.2. Function of magnesium

2.2.1. Biochemical functions

Magnesium is a cofactor of more than 300 enzymatic reactions, acting either on the substrate (especially for reactions involving ATP, where its binding to the nucleotide induces an adequate conformation and helps to weaken the terminal O–P bond of ATP, thereby facilitating the transfer of phosphate (Sanders et al., 1999; Rude and Gruber, 2004)) or on the enzyme itself as a structural or catalytic component. As ATP utilisation is involved in many metabolic pathways, magnesium is essential in the intermediary metabolism for the synthesis of carbohydrates, lipids, nucleic acids and proteins, as well as for specific actions in various organs such as the neuromuscular or cardiovascular system. Magnesium can interfere with calcium at the membrane level or bind to membrane phospholipids, thus modulating membrane permeability and electrical characteristics. Magnesium has an impact on bone health through its role in the structure of hydroxyapatite crystals in bone.

2.2.2. Health consequences of deficiency and excess

2.2.2.1. Deficiency

Magnesium deficiency can have many different causes, including renal and gastrointestinal dysfunctions; magnesium deficiency can cause hypocalcaemia and hypokalaemia, leading to neurological or cardiac symptoms when it is associated with marked hypomagnesaemia (< 0.5 mmol/L). Owing to the widespread involvement of magnesium in numerous physiological functions and the metabolic interactions between magnesium and other minerals, it is difficult to relate magnesium deficiency to specific symptoms such as neuromuscular irritability, muscle tremors and cramps, fasciculation, wasting and weakness, restless leg syndrome, fibromyalgia, i.e. conditions where the use of magnesium supplementation has led to inconsistent results (Brown et al., 2012).

2.2.2.2. Excess

A Tolerable Upper Intake Level (UL) was determined by the SCF (2001) based on studies in which mild diarrhoea occurred after ingestion of magnesium supplements and in which information on magnesium intake from foods and beverages was not available. A No Observed Adverse Effect Level (NOAEL) of 250 mg/day was derived and, using an uncertainty factor of 1, a UL of 250 mg/day was established for adults, including pregnant and lactating women, and children from 4 years of age and

older. Owing to a lack of data, a UL could not be established for children aged 1–3 years. The UL was established for readily dissociable magnesium salts (e.g. chloride, sulphate, aspartate, lactate) and compounds such as magnesium oxide in nutritional supplements or water, or added to foods and beverages, but does not include magnesium normally present in foods and beverages.

2.3. Physiology and metabolism

2.3.1. Intestinal absorption

Magnesium absorption takes place in the distal small intestine, mainly in ionised form through a paracellular process via tight junctions and is driven by electrochemical gradients and solvent drag. Saturable transcellular absorption seems to be significant only at low dietary intakes. At usual intakes, magnesium absorption is only loosely regulated; percentage absorption is generally considered to be 40–50 %, but figures from 10 to 70 % have also been reported. The fractional absorption of magnesium decreases with increasing magnesium intake, which makes the comparison between studies difficult (Sabatier et al., 2003a). Magnesium absorption can be inhibited by phytic acid and phosphate and enhanced by the fermentation of soluble dietary fibre, although the physiological relevance of these interactions at intakes considered to be adequate remains to be established.

2.3.2. Transport in blood

Approximately 0.3 % of body magnesium is in the serum, as free cations (about 54 %), which is the bioactive form, as a protein-bound form (about 33 %, mainly to albumin (75 %)) and as anion complexes (about 13 %) (Elin, 1987). Magnesium concentrations in blood cells are higher than in the serum: eight times in reticulocytes, three times in red blood cells.

2.3.3. Distribution to tissues

Magnesium is approximately equally distributed in bone and soft tissues, less than 1 % being present in blood compartments. Cellular magnesium concentrations are constantly in the range of 17–20 mmol/L (Swaminathan, 2003), despite rapid movements across cell membranes through multiple carriers and channels. Intracellular concentrations have been observed to decrease linearly with increasing age, without parallel changes in plasma magnesium concentration (Barbagallo et al., 2000; Barbagallo et al., 2009).

The most important transport system to tissues appears to be the transient receptor potential melastatin 7 (TRPM7), associated with cell proliferation or apoptosis; TRPM7, which is also permeable to calcium, is negatively regulated by intracellular magnesium and magnesium–nucleotide complexes (Romani, 2011; Park et al., 2014). TRPM6, functioning with TRPM7 or independently, is specifically expressed in the colon and distal renal tubule, where it plays a role in the reabsorption of magnesium (Woudenberg-Vrenken et al., 2009; Romani, 2011). Some other non-specific transporters are also involved in magnesium transfer, such as claudins, MagT1, SLC41, ACDP, NIPA and Huntingtin across cell membranes, Mrs2 across mitochondrial membranes and MMgt across Golgi membranes (Romani, 2011). As shown in *in vitro* studies, through the action of magnesium transporters enabling large magnesium fluxes, most cells are able to actively and rapidly buffer magnesium loss or accumulation (Romani, 2011). In the whole body, compartmental analysis using stable isotopes showed the existence of at least two major extraplasma compartments: the first compartment represents 80 % of the rapidly exchangeable pool with an exchange rate of 48 mg/hour; the second pool has a faster exchange rate of 179 mg/hour; the sum of these rapidly exchangeable compartments amounts to around 25 % of the magnesium body pool (Sabatier et al., 2003b).

2.3.4. Storage

Total body magnesium content in a healthy adult is around 20–28 g (Rude, 2014). Of this, about 60 % is in bone (Swaminathan, 2003; Musso, 2009), either strongly bound to apatite, where it is difficult to mobilise, or loosely adsorbed at the surface of mineral crystals, where it can be easily mobilised in response to variation in dietary supply (Laires et al., 2004). About 25 % of body magnesium is in

muscle, where mitochondria are considered to be the intracellular storage site (Kubota et al., 2005; Wolf and Trapani, 2008).

2.3.5. Elimination

2.3.5.1. Urine

The kidney plays a major role in magnesium homeostasis and maintenance of serum concentrations. Around 80 % of serum magnesium is ultrafiltrable through the glomerulus, but only around 3 % of the filtered fraction appears in the urine, owing to an efficient reabsorption taking place mainly (60–70 %) in the thick ascending loop of Henle. This transport is directly related to sodium chloride reabsorption and the positive luminal voltage in this segment. The main stimuli that increase urinary magnesium excretion are high natriuresis, osmotic load and metabolic acidosis; those that reduce it are metabolic alkalosis, parathyroid hormone and, possibly, calcitonin (Musso, 2009). The remaining part of the reabsorption takes place in the distal convoluted tubule via an active transcellular mechanism that finally controls the amount excreted in the urine (Dai et al., 2001).

2.3.5.2. Faeces

A large proportion of the magnesium content of faeces stems from unabsorbed magnesium (Lakshmanan et al., 1984). The endogenous routes of elimination of absorbed magnesium through the digestive tract are bile, pancreatic and intestinal juices, and intestinal cells; part of these endogenous losses can be reabsorbed (Swaminathan, 2003). Using stable isotopes, endogenous faecal excretion has been determined to be 49 ± 11 mg/day in six healthy men aged 26–41 years (Sabatier et al., 2003b), around 15 mg/day (0.1–0.9 mg/kg body weight per day) in 9- to 14-year-old boys and girls (Abrams et al., 1997) and from 4.7 to 21.7 mg/day in five girls aged 12–14 years, without influence of calcium intake (Sojka et al., 1997).

From a compilation of balance studies in adults (Hunt and Johnson (2006); see Section 5.2.1) basal urinary and faecal losses may be deduced as losses at zero intake; these amounted to around 20 mg/day (around 0.31 mg/kg body weight per day).

2.3.5.3. Skin and sweat

Reported sweat magnesium concentrations are very variable, ranging from 3 to 60 mg/L depending on the environment, with a hot and humid environment associated with the highest losses (Nielsen and Lukaski, 2006). After 24-hour exposure to 37 °C, sweat losses amounted to 25 % of the total daily magnesium loss (Consolazio et al., 1963). Acclimation may reduce sweat magnesium concentrations by around 40 % (Chinevere et al., 2008), although this finding may have been due to technical issues rather than an adaptive physiological process (Ely et al., 2013). Costa et al. (1969) measured during exercise a sweat magnesium concentration of around 15 µg/g. During exercise in a hot environment (27 °C), Beller et al. (1975) determined the magnesium concentration of sweat to range from 1.6 to 5.4 mg/L. Using a different technique for collecting the totality of sweat, Shirreffs and Maughan (1997) measured a concentration of 12.2 ± 12.2 mg/L during four repeated trials in five healthy young men and women. Montain et al. (2007) determined a sweat magnesium concentration of 1.3 ± 0.6 mg/L in seven heat-acclimated subjects (six males, one female) completing several hours of treadmill exercise at 27 °C.

In 7- to 9-year-old boys involved in sedentary activities in a metabolic unit, magnesium total body sweat loss was very variable but also very low, ranging from 16 to 300 µg/day, with a mean of 115 µg/day. Mean and maximum loss represented only 0.05 and 0.13 %, respectively, of the intake (range 179–300 mg/day) (Harrison et al., 1976). Daily loss through sweat was found to be around 2 mg/day (0.6 % of the total output) in six men (McDonald and Margen, 1979). In six healthy women aged 27 ± 4 years, a whole-body magnesium loss of 35 ± 13 mg/day was measured; in this experiment, a patch technique was shown to overestimate magnesium sweat loss by 3.6 times (Palacios et al., 2003). Whole-body sweat magnesium concentration was 9.8 ± 4.8 mg/L for seven men and women

exercising for 90 minutes at 30°C, the patch technique overestimating this value by 48 % (Baker et al., 2011).

Hunt and Johnson (2006) reported on whole-body surface losses of magnesium in 11 young men. Subjects wore cotton suits for 48 hours, after which time their skin was rinsed with deionised water. Whole-body surface losses of 4.1 mg/day were measured and considered to be negligible.

The Panel notes that very different figures have been reported for magnesium sweat losses, which can be at least partially explained by different techniques for sweat collection; the highest values are reported after intense exercise and/or in a hot environment. At moderate physical activity performed around thermoneutrality, the Panel considers that magnesium losses through sweat are likely to be modest, in the range of 1–5 mg/day, on the basis of a daily sweat volume of around 0.5 L/day (Shirreffs and Maughan, 2005; Subudhi et al., 2005).

2.3.5.4. Menses

Hunt and Schofield (1969) measured menstrual magnesium losses in five women (20–40 years of age); for the whole menstrual period, these varied from 2 ± 1 mg to 7 ± 5 mg in different experimental settings. On a daily basis, this loss appears to be marginal. Hunt and Johnson (2006) reported on menstrual magnesium losses amounting to 2.3 mg/day, with a range of 0.3–6.5 mg/day, although the source of these data is unclear. Considering a magnesium concentration in whole blood of around 35–40 mg/L in healthy women in the control group (Abdulsahib, 2011) and the volume of blood loss (median 18–30 mL per menstrual period (Hallberg et al., 1966; Harvey et al., 2005)), a median magnesium loss of around 0.6–1.2 mg/menstrual period can be calculated.

The Panel considers that magnesium losses through menstruation in women are negligible.

2.3.5.5. Breast milk

Two comprehensive literature searches were performed on breast milk magnesium concentrations (periods January 1990 to October 2011 (Brown et al., 2012) and October 2010 to January 2014 (LASER Analytica, 2014)). These searches identified 16 studies on magnesium concentration in breast milk of mothers of term infants, one of which was a review (Dorea, 2000). Studies not yet considered in the review by Dorea (2000) are listed in Appendix A.

The studies report cross-sectional sample data from 1–365 days of lactation. Mean magnesium concentration from all breast milk studies ranged between 23 and 35 mg/L, in line with the conclusion of the review by Dorea (2000), where a median value of 31 mg/L from a range of 15 to 64 mg/L is provided. Dorea (2000) indicated that 75 % of reported mean magnesium concentrations in breast milk were below 35 mg/L. Variation is probably due to different analytical techniques employed within studies and differences in dietary patterns between countries (Parr et al., 1991).

For the studies listed in Appendix A, there was no clear correlation between stage of lactation and breast milk magnesium concentration. Hunt et al. (2005) found that there was a relatively wide variation between subjects at a given stage of lactation.

Dengel et al. (1994) provided a controlled diet (218 mg/day) to six lactating, six non-lactating and seven never-pregnant women; from measurement of magnesium concentration in breast milk (33.3 ± 0.2 mg/L) and estimation of infant's intake by test weighing, it was concluded that 25.2 ± 1.5 mg/day of magnesium was provided to the infant via breast milk.

The Panel considers that the magnesium concentration of mature human milk is 31 mg/L. Based on a mean milk transfer of 0.8 L/day (Butte et al., 2002; FAO/WHO/UNU, 2004; EFSA NDA Panel, 2009) and a concentration of magnesium in mature breast milk of 31 mg/L, a secretion of 25 mg/day of magnesium in breast milk is estimated during the first six months of lactation.

2.3.6. Interaction with other nutrients

On the basis of physiology, metabolism and biochemistry, many interactions of magnesium with other minerals, vitamins or substances present in foods can be suspected, some of which have already been mentioned; most of these interactions have been the subject of a very limited number of studies, frequently with a high risk of bias (Brown et al., 2012). Balance studies performed either in children or in adults did not detect an interaction between magnesium and calcium balances (Greger et al., 1978; Spencer et al., 1994; Andon et al., 1996; Abrams et al., 1997; Milne and Nielsen, 2000; Klevay and Milne, 2002). However, in two studies, calcium balance was significantly higher under conditions of negative magnesium balance (at magnesium intakes of 107 and 118 mg/day) than with a positive magnesium balance (at magnesium intakes of 318 and 327 mg/day) (Nielsen, 2004; Nielsen et al., 2007). An intake of 53 mg zinc/day over 90 days can decrease magnesium balance (Nielsen and Milne, 2004).

There are some studies indicating a relationship with protein intake, possibly through increased apparent magnesium absorption. For example, in boys aged 13–14 years, Schwartz et al. (1973) showed that zero magnesium balance was obtained with an intake of 4.6 mg/kg body weight per day for a high-protein diet (265 mg nitrogen/kg body weight per day, i.e. 1.65 g protein/kg body weight per day) and with an intake of 7.6 mg/kg body weight per day for a low-protein diet (123 mg nitrogen/kg body weight per day, i.e. 0.77 g protein/kg body weight per day⁶) (see Appendix H). The balance study of Wisker et al. (1991) showed that percentage faecal magnesium excretion and balances differed significantly between low-fibre and high-fibre diets containing adequate amounts of protein; in the study of Kelsay and Prather (1983) there was no clear effect of diets low and high in fibre and oxalic acid on magnesium balances.

Manganese shares physical properties with magnesium that enable it to be interchangeable with magnesium in enzymatic phosphate transfer reactions and it has been used as a probe to study the role of magnesium in these processes, particularly in energy metabolism. The relevance of this inter-relationship to human dietary requirements is uncertain, but it is noteworthy that pigs fed 25 % of the recommended intake of magnesium had an increased incidence of cardiac changes and sudden death (Miller et al., 2000).

The Panel considers that data on interactions between magnesium and other minerals, protein or fibre are limited and cannot be used for setting Dietary Reference Values (DRVs) for magnesium.

2.4. Biomarkers

For the assessment of magnesium status, the concentrations of magnesium in urine, faeces, serum and erythrocytes have been measured. Witkowski et al. (2011) assessed methods for determining magnesium status in humans and undertook meta-analyses. This systematic review included a total of 27 studies (randomised controlled trials, controlled trials, depletion–repletion studies or depletion-only studies). However, conclusions about the responsiveness of the identified relevant biomarkers and type, dose or length of supplementation were not possible and there was a high degree of heterogeneity between studies.

2.4.1. Serum/plasma magnesium concentration

The sensitivity of serum/plasma magnesium concentration to magnesium intake is low. Combining data from 18 supplementation arms (doses of 197 mg/day to 23 mg/kg body weight per day for 3–52 weeks) and four depletion–repletion or depletion-only studies with 322 participants, Witkowski et al. (2011) showed a significant response of serum/plasma magnesium concentration to magnesium intake for all studies. However, the depletion–repletion or depletion-only studies did not reveal changes in serum/plasma magnesium concentration in response to changes in magnesium intake. Others have noted a lack of association between magnesium intake via self-selected diets and plasma magnesium

⁶ The PRI for protein for boys aged 13 years is 0.9 g/kg body weight per day and it is 0.89 g/kg body weight per day for boys aged 14 years (EFSA NDA Panel, 2012).

concentration (Lakshmanan et al., 1984). In the study of Misialek et al. (2013), when stratifying for serum magnesium concentration and relating this to magnesium intake, the quintiles of serum magnesium concentration correspond to similar average magnesium intakes, i.e. from 247 to 258 mg/day, whereas the quintiles of dietary intake range from < 181 mg/day to ≥ 320 mg/day.

Serum magnesium concentration remains within a narrow range. Based on data from the US National Health and Nutrition Examination Survey I (5th and 95th percentiles), Lowenstein and Stanton (1986) have suggested that values below 0.75 mmol/L may indicate magnesium deficiency and values above 0.96 mmol/L may indicate excessive intakes. However, it has also been suggested that a serum magnesium concentration within this range cannot totally rule out the possibility of magnesium deficiency (Arnaud, 2008). Serum magnesium concentration remains constant with increasing age (Barbagallo et al., 2009).

Thus, despite serum/plasma magnesium concentration being the most frequently used biomarker for magnesium, the Panel considers that the usefulness of serum/plasma magnesium concentration as a marker of intake or status is questionable.

Theoretically, the concentration of ionised magnesium in plasma, serum or blood would be a better marker of functional magnesium. However, the information is limited and the few studies available did not indicate that ionised magnesium concentration changes in response to changes in magnesium intake (Durlach et al., 2002; Witkowski et al., 2011).

2.4.2. Red blood cell magnesium concentration

Erythrocytes contain a high concentration of magnesium (2.3 ± 0.24 mmol/L of packed cells; ionised magnesium 0.2 ± 0.2 mmol/L of cell water (Millart et al., 1995)), which is required for ATP utilisation and some other metabolic functions. The relationship between magnesium intake and red blood cell magnesium concentration has been described as weak (Lakshmanan et al., 1984). Several weeks of low magnesium intake are needed for red blood cell magnesium concentration to decrease, so that this marker may reflect medium-term magnesium status.

Compared with red blood cell magnesium concentration, magnesium concentration in platelets or lymphocytes may better reflect muscle and tissue concentrations (Arnaud, 2008). However, Witkowski et al. (2011) point out the paucity of available information in humans.

2.4.3. Urinary magnesium excretion

Magnesium intake (duplicate diet analysis of self-selected diets) and urinary magnesium concentration have been found to be correlated ($r = 0.45$) (Lakshmanan et al., 1984). According to Witkowski et al. (2011), the combination of data from 15 supplementation arms (with doses between 200 mg magnesium given once and 23 mg/kg body weight per day given for 52 weeks) and three depletion–repletion or depletion-only studies including 363 subjects revealed a significant response of urinary magnesium excretion to a change in magnesium intake, although there was considerable heterogeneity between studies. The authors stressed that the low number of studies with few subjects per study precludes conclusions to be drawn about potential relations between biomarker responsiveness and type, dose or length of supplementation. Moreover, magnesium intake from diet alone is not reported in all supplementation studies.

2.4.4. Other potential biomarkers

The magnesium loading test has been proposed as a marker of magnesium status: when 24-hour urinary excretion of magnesium after a magnesium load is decreased, this is interpreted as an indicator of magnesium deficiency; however, there is no standardised protocol (Arnaud, 2008) and no consensus on the usefulness of the test (Elin, 2011; Günther, 2011). Similarly, hair and nail magnesium concentrations are difficult to interpret, as the relationship with intake, deficiency or excess is still unclear (Arnaud, 2008).

Tissue magnesium concentrations (e.g. muscle) require invasive techniques and have not been frequently measured in human studies; non-invasive techniques such as neutron activation measuring magnesium in hand bones still require validation in clinical studies (Aslam et al., 2008).

Although magnesium is the cofactor of many enzymes, no functional biomarker has been identified to date; however, fasting C-peptide and plasma insulin concentrations have been proposed as possible markers following a study using a dose of supplemental magnesium above the UL (Chacko et al., 2011). The Panel notes the lack of specificity of these parameters for magnesium status.

2.4.5. Conclusions on biomarkers of intake and status

Reviews on biomarkers of magnesium intake or status generally conclude that all the proposed markers have limitations (Elin, 1987, 1991; Franz, 2004; Arnaud, 2008; Witkowski et al., 2011). The Panel considers that there are at present no appropriate biomarkers for magnesium status. The Panel also considers that the suitability of urinary magnesium excretion as a marker of intake requires confirmation in well-designed studies.

2.5. Effects of genotype

From twin studies, heritability of magnesium control appears to be limited (only 27 % of the variance may be genetically determined) (Hunter et al., 2002) and the underlying genetic control system might be complex (Henrotte et al., 1990). Several genetic disorders of magnesium homeostasis have been characterised in a limited number of affected individuals (Weber et al., 2001; Schlingmann et al., 2004). Genome-wide association studies have identified several loci that influence serum magnesium concentrations (Meyer et al., 2010). Some common genetic variants of TRPM6 and seven genes have been associated with a higher risk of diabetes mellitus type 2 when magnesium intake is below 250 mg/day (Song et al., 2009), but this has not been confirmed in a large-scale study combining the data from 15 prospective cohorts (Hruby et al., 2013). The Panel considers that there is currently no basis for taking into account the information on genotypes for the setting of DRVs for magnesium.

3. Dietary sources and intake data

3.1. Dietary sources

Foods rich in magnesium are nuts, whole grains and grain products, fish and seafood, several vegetables, legumes, berries, banana and some coffee and cocoa beverage preparations. The magnesium content of tap/bottled water can make a significant contribution to intake.

Currently, magnesium as magnesium acetate, magnesium carbonate, magnesium chloride, magnesium salts of citric acid, magnesium gluconate, magnesium glycerophosphate, magnesium salts of orthophosphoric acid, magnesium lactate, magnesium hydroxide, magnesium oxide, magnesium potassium citrate and magnesium sulphate may be added to both foods⁷ and food supplements,⁸ whereas magnesium L-ascorbate, magnesium bisglycinate, magnesium L-lysinate, magnesium malate, magnesium L-pidolate, magnesium pyruvate, magnesium succinate, magnesium taurate and magnesium acetyl taurate may be added to food supplements only.⁶ The magnesium content of infant and follow-on formulae⁹ and the maximum magnesium content of processed cereal-based foods and baby foods for infants and young children¹⁰ is regulated.

⁷ Regulation No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods. OJ L 404, 30.12.2006, p. 26.

⁸ Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. OJ L 183, 12.7.2002, p. 51.

⁹ Commission Directive 2006/141/EC of 22 December 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC. OJ L 401, 30.12.2006, p. 1.

¹⁰ Commission Directive 2006/125/EC of 5 December 2006 on processed cereal-based foods and baby foods for infants and young children. OJ L 339, 6.12.2006, p. 16.

3.2. Dietary intake

EFSA estimated dietary intake of magnesium from food consumption data from the EFSA Comprehensive European Food Consumption Database (EFSA, 2011b), classified according to the food classification and description system FoodEx2 (EFSA, 2011a). Food consumption data from 13 dietary surveys from nine European Union (EU) countries (Finland, France, Germany, Ireland, Italy, Latvia, the Netherlands, Sweden and the UK) were used. The data covered all age groups from infants to adults aged 75 years and older (Appendix B).

Nutrient composition data for magnesium were derived from the EFSA Nutrient Composition Database (Roe et al., 2013). Food composition information from Finland, France, Germany, Italy, the Netherlands, Sweden and the UK was used to calculate magnesium intake in these countries, assuming that the best intake estimate would be obtained when both the consumption data and the composition data are from the same country. For magnesium intake estimates for Ireland and Latvia, food composition data from the UK and Germany, respectively, were used, because no specific composition data from these countries were available. In the event of missing values in a food composition database, data providers had been allowed to borrow values from another country's database. The amount of borrowed magnesium values in the seven composition databases used varied between 14 % and 91 %. A magnesium value was missing for all included countries for 673 consumed food items, for which imputation of missing composition values was undertaken by EFSA. Magnesium intake calculations were performed only on subjects with at least two reporting days. EFSA intake estimates are based on the consumption of foods, either fortified or not (i.e. without consideration of dietary supplements).

Food consumption data of infants (aged 1 to < 12 months in the Italian INRAN-SCAI survey, 4 to < 12 months in the UK DNSIYC survey, 6 months in the Finnish DIPP study and 6 to < 12 months in the German VELs survey, for full names of all surveys, see Abbreviations) were provided by four studies. The consumption of human milk was taken into account if the amount of human milk consumed (Italian INRAN-SCAI survey and UK DNSIYC survey) or the number of breast milk consumption events (German VELs survey) were reported. In the case of the Italian INRAN-SCAI survey, the data provider had estimated the human milk consumption prior to submitting the data to EFSA based on the number of eating occasions using standard portions per eating occasion. In the Finnish DIPP study, only the information "breast fed infants" was available, but without any indication of the number of breast milk consumption events or the amount of breast milk consumed per event. For the German VELs study, the total amount of breast milk was calculated based on the observations by Paul et al. (1988) on breast milk consumption during one eating occasion at different ages, i.e. the amount of breast milk consumed on one eating occasion was set to 135 g/eating occasion for infants aged 6–7 months and to 100 g/eating occasion for infants aged 8–12 months. The Panel notes the limitations in the methods used for assessing breast milk consumption in infants (Appendices C and D) and related uncertainties in the intake estimates for infants.

Magnesium intake was calculated in mg/day, mg/MJ (Appendices C and D) and mg/kg body weight per day for males and females. For both sexes combined, average magnesium intake ranged from 72 to 120 mg/day (25–45 mg/MJ, 9.2–12.7 mg/kg body weight per day) in infants (< 1 year of age, four surveys); from 153 to 188 mg/day (35–45 mg/MJ, 12.7–15.8 mg/kg body weight per day) in children aged 1 to < 3 years (five surveys); from 184 to 281 mg/day (28–43 mg/MJ, 7.6–13.0 mg/kg body weight per day) in children aged 3 to < 10 years (seven surveys); from 213 to 384 mg/day (28–44 mg/MJ, 4.2–7.7 mg/kg body weight per day) in children aged 10 to < 18 years (seven surveys); and from 232 to 439 mg/day (35–51 mg/MJ, 3.4–5.3 mg/kg body weight per day) in adults of both sexes (≥ 18 years, eight surveys). Average daily intake (but not energy-adjusted intake) was, in most cases, slightly higher in males (Appendix C) than in females (Appendix D), mainly owing to larger quantities of food consumed per day.

The main food groups contributing to magnesium intake were grains and grain-based products (up to 20–40 % in all groups except infants), milk and dairy products (up to about 10–30 % of the total

magnesium intake in children and less in older age classes) and coffee, cocoa, tea and infusions (up to about 20 % in adults) (see Appendices E and F). Differences in the main contributors to magnesium intake between males and females were small.

EFSA's magnesium intake estimates in mg/day were compared with published intake values, where available, from the same survey and dataset and the same age class, using the German EsKiMo and VELS surveys in children (Kersting and Clausen, 2003; Mensink et al., 2007), the DIPP study in Finnish children (Kyttälä et al., 2008; Kyttälä et al., 2010), the study in Finnish adolescents (Hopppu et al., 2010), the French INCA2 survey (Afssa, 2009), the Irish NANS (IUNA, 2011), the Finnish FINDIET 2012 Survey (Helldán et al., 2013), the Italian INRAN-SCAI survey (Sette et al., 2011), the Dutch National Food Consumption Survey (van Rossum et al., 2011), the Swedish national survey Riksmaten (Amcoff et al., 2012), the UK NDNS (Bates et al., 2012) and the DNSIYC-2011 Study in UK infants and toddlers (Lennox et al., 2013). EFSA's intake estimates for the various surveys compared with published values are shown in Table 1. Values below 100 % indicate that EFSA's intake estimates are lower than published values and values above 100 % indicate the opposite.

Table 1: EFSA's average magnesium intake estimates, expressed as percentages of published intake

Country	% of published intake, range over different age classes in a specific survey
Finland	93–110 % (DIPP, for ages ≥ 1 year), 105–106 % (Finnish adolescents), 94–97 % (FINDIET 2012)
France	96–109 % (INCA2)
Germany	82–86 % (VELS infants), 100–108 % (VELS children), 94–99 % (EsKiMo)
Ireland	111–120 % (NANS)
Italy	91 % (INRAN-SCAI, infants and children aged 1 to < 3 years), 104–108 % (children aged 3 to < 18 years), 117–121 % (adults)
Netherlands	96–98 % (Dutch National Food Consumption Survey)
Sweden	113–119 % (Riksmaten)
UK	120–123 % (DNSIYC-2011), 108–118 % (NDNS Rolling Programme Years 1–3, for ages ≥ 3 years)

Comparisons had inherent limitations in the case of the UK survey, where published intake values covered the first two years of the survey and EFSA data from the UK covered the first three years. In the survey in Finnish children aged 10–18 years, published values were for two consecutive days of dietary recall, while EFSA data comprised two 48-hour dietary recalls. Likewise, comparisons were not optimal for the German EsKiMo study and the Finnish DIPP study, because the published intake values included supplement consumption, while the EFSA estimates are based on food consumption only. However, according to these publications (Mensink et al., 2007; Kyttälä et al., 2010), magnesium supplements were not among the major contributors to magnesium intake in these age classes. A comparison could not be undertaken for the Latvian survey or the infants in the Finnish DIPP study, as no matching publication was available. The EFSA estimates differed by up to about 10 % from the published values in Finland, France, Germany and the Netherlands. For infants in the German VELS study, the intakes were underestimates of 14–18 %. This is most probably due to differences in the composition data used for the intake estimations, because the quantification of breast milk consumption was done similarly in the VELS study and in this assessment (Paul et al., 1988; Kersting and Clausen, 2003). The estimated Irish intakes were found to be higher by 11–20 % than published estimates, which may partly be because data provided on composite dishes were almost completely disaggregated to ingredient level, thereby not capturing possible magnesium losses owing to processing. EFSA intake estimates were also higher than published magnesium estimates for Sweden and the UK, which may partly be related to the high number of composite foods in these datasets, for which the national magnesium values for composite foods may have been more accurate than values of the somewhat limited list of composite foods in the FoodEx2 classification system.

Uncertainties in the estimates of all countries may be caused by inaccuracies in mapping food consumption data according to the FoodEx2 classification system, analytical errors or errors in the

estimation of the concentration in foods in the food composition databases, the use of borrowed magnesium values from other countries in the food composition databases and the replacement of missing magnesium values by available values for similar foods or food groups in the magnesium intake estimation process. These uncertainties may, in principle, lead to estimates of magnesium intake that are both too high and too low. It is not possible to conclude which of these intake estimates (i.e. the EFSA intake estimate or the published one) would be closer to the actual magnesium intake.

4. Overview of Dietary Reference Values and recommendations

4.1. Adults

The German-speaking countries (D-A-CH, 2015) derived Recommended Intakes (RIs) based on results of balance studies (Jones et al., 1967; Marxhall et al., 1976; Lakshmanan et al., 1984; Wisker et al., 1991; IOM, 1997) and urinary magnesium excretion before and after magnesium loading in older adults (Gullestad et al., 1994).

Previously, the Nordic countries had set RIs of 350 mg/day for men and 280 mg/day for women. For this, evidence from a balance study had been considered to show that a magnesium intake of 3.4 mg/kg body weight per day resulted in neutral magnesium balance in almost all subjects (Jones et al., 1967). For the Nordic Nutrition Recommendations (NNR) 2012, it was considered that the new evidence, including a pooled analysis of 27 balance studies (Hunt and Johnson, 2006) pointing to neutral magnesium balance at lower intakes than these RIs, does not indicate that the values should be changed (Nordic Council of Ministers, 2014).

The World Health Organization/Food and Agriculture Organization of the United Nations (WHO/FAO, 2004) highlighted the uncertainties in previously used approaches to derive magnesium requirements. It was also stated that previous estimates by other authorities may have been overestimates. Based on magnesium intake on a body weight basis considered by similar committees in the USA, the EU and the UK to maintain zero magnesium balance and considering, in particular, balance studies enabling the development of an equilibrium (Hunt and Schofield, 1969; Marxhall et al., 1976; Mahalko et al., 1983; Andon et al., 1996), Recommended Nutrient Intakes were proposed which were denoted as provisional. WHO/FAO (2004) assumed that older adults have a lower requirement “as requirements for growth diminish”, but that at the same time absorption efficiency probably decreases as well.

On the basis of data from balance studies (Lakshmanan et al., 1984; Spencer et al., 1994), the French Food Safety Agency (Afssa, 2001) determined an Average Requirement (AR) for adults of 350 mg/day or 5 mg/kg body weight per day. By applying a coefficient of variation (CV) of 10 %, a PRI of 6 mg/kg body weight per day was set.

On the basis of balance studies conducted in men (Greger and Baier, 1983; Lakshmanan et al., 1984; Schwartz et al., 1986) and women (Lakshmanan et al., 1984; Wisker et al., 1991), IOM (1997) derived Estimated Average Requirements (EARs) of 330 mg/day for men and 255 mg/day for women aged 19 to 30 years. Applying a CV of 10 % to these EARs resulted in Recommended Dietary Allowances (RDAs) of 400 and 310 mg/day for men and women, respectively. For men aged 31–50 years, balance studies of Kelsay et al. (1979); Kelsay and Prather (1983); Mahalko et al. (1983); Lakshmanan et al. (1984) and Spencer et al. (1994) were considered. As there were more instances of negative balance in the intake range of 300–350 mg/day for subjects in this age range, the EAR was set at a slightly higher amount, i.e. at 350 mg/day. For men aged 51–70 years, the aforementioned balance studies plus one study in men with a mean age of 53 ± 5 years were considered (Schwartz et al., 1984) and the same EAR of 350 mg/day was derived. For women aged 31–50 and 51–70 years, the EAR was raised to 265 mg/day based on the study by Lakshmanan et al. (1984) and considering the slight increase for men of these age ranges compared with younger men. RDAs of 420 and 320 mg/day were derived for men and women aged 31–70 years, respectively. For adults over 70 years of age, results from balance studies were not available and results from magnesium tolerance tests and red blood cell magnesium

concentrations were considered. Given the uncertainty of these markers as indicators of magnesium requirement and the lack of balance studies for older adults, it was decided that the EAR and the RDA for adults aged 31–70 years would also be retained for this age group.

The SCF (1993) noted that results of balance studies are difficult to interpret owing to methodological limitations in some studies, and to a long time to achieve equilibrium and the potential for physiological adaptations to low magnesium intakes (Marxhall et al., 1976; Seelig, 1982; Schwartz et al., 1984). It was stated that some balance data suggest that a magnesium intake of 3.4 mg/kg body weight per day may be associated with zero balance (Jones et al., 1967; Health and Welfare Canada Scientific Review Committee, 1990), but a PRI was not set. Instead, an Acceptable Range of Intakes of 150–500 mg/day was proposed based on observed intakes (in the USA and the UK).

The Netherlands Food and Nutrition Council (1992) considered, on the basis of balance studies (Jones et al., 1967; Schwartz et al., 1978; Kelsay et al., 1979; van Dokkum et al., 1983; Schwartz et al., 1984), that no negative balances occur at magnesium intakes of 250–350 mg/day. Assuming that magnesium requirement is related to body weight, an Adequate Range of Intake of 300–350 mg/day for men and of 250–300 mg/day for women was derived.

The UK Committee on Medical Aspects of Food Policy (COMA) (DH, 1991) considered balance studies to set DRVs (Jones et al., 1967; Marxhall et al., 1976; Seelig, 1982). Based on one study (Jones et al., 1967) showing that a magnesium intake of 3.4 mg/kg body weight per day is adequate for maintaining zero balance, an EAR was derived by multiplication with reference body weights. Using a CV of 10 % for men and 17.5 % for women, Reference Nutrient Intakes were set for men and women of all ages (Table 2).

Table 2: Overview of Dietary Reference Values for magnesium for adults

	D-A-CH (2015)	NCM (2014)	WHO/FAO (2004)	Afssa (2001)	IOM (1997)	SCF (1993)	NL (1992)	DH (1991)
Age (years)	19–< 25	≥ 18	19–65	≥ 20	19–30	≥ 18	≥ 19	≥ 19
PRI								
Men (mg/day)	400	350	260	420	400	150–500 ^(a)	300–350 ^(a)	300
Women (mg/day)	310	280	220	360	310	150–500 ^(a)	250–300 ^(a)	270
Age (years)	≥ 25		> 65		≥ 31			
PRI								
Men (mg/day)	350		224		420			
Women (mg/day)	300		190		320			

NCM, Nordic Council of Ministers; NL, Netherlands Food and Nutrition Council.

(a): Acceptable/Adequate Range of Intake(s).

4.2. Infants and children

The German-speaking countries (D-A-CH, 2015) assumed that there is a magnesium retention of 3 mg/kg body weight per day during growth, which should be covered by an intake of 6 mg/kg body weight per day (IOM, 1997). RIs were derived on the basis of this value and taking into account reference body weights of the age groups (Table 3).

For NNR 2012, the Nordic countries (Nordic Council of Ministers, 2014) maintained the RIs for children from 1996, which at that time had been taken over from the SCF (1993).

WHO/FAO (2004) stated that results of magnesium balance studies and other studies possibly useful for assessing magnesium requirements should be interpreted in the light of protein and energy intakes of subjects studied. It was also stated that previously derived magnesium requirements by other authorities may have been overestimates. Based on magnesium intake on a body weight basis considered by similar committees in the USA, the EU and the UK to maintain zero magnesium balance and considering, in particular, balance studies enabling the development of an equilibrium (Hunt and Schofield, 1969; Marxhall et al., 1976; Mahalko et al., 1983; Andon et al., 1996),

Recommended Nutrient Intakes were proposed which were denoted as provisional. The results of a study on nutritional rehabilitation of children suffering from protein–energy malnutrition who were receiving or not receiving magnesium supplements (Nichols et al., 1978) were considered to support the value derived for young children.

Afssa (2001) set an AI of 75 mg/day for infants from 6 to 12 months of age on the basis of magnesium intake from breast milk and solid food (Lönnerdal, 1995). Afssa (2001) noted that studies using isotopes indicate an AR of 5 mg/kg body weight per day for children (Abrams et al., 1997), which increases to 5.3 mg/kg body weight per day in older children because of an increase in growth velocity. The PRI of 6 mg/kg body weight per day derived for adults was also applied to children up to 12 years of age. For children aged 13–18 years, an additional intake of 25 mg/day was advised to cover needs related to the increased rate of growth.

IOM (1997) set an AI of 75 mg/day for infants aged 7–12 months considering an average magnesium concentration in breast milk of 34 mg/L (Dewey et al., 1984; Allen et al., 1991), a mean breast milk intake of 0.6 L/day (Heinig et al., 1993) and a mean magnesium intake from solid foods of 55 mg/day as observed in formula-fed infants aged 9–12 months (Specker et al., 1997). For children from 1 to 18 years of age, EARs were set on the basis of magnesium balance studies. These were available for children aged 10–15 years (Schwartz et al., 1973; Greger et al., 1978; Greger et al., 1979; Andon et al., 1996; Abrams et al., 1997; Sojka et al., 1997) and 7–9 years (Schofield and Morrell, 1960). A magnesium intake of 5 mg/kg body weight per day appeared to have met the requirement of some but not all children in these studies. Using this value and reference body weights, EARs for younger children were extrapolated and were 65, 110 and 200 mg/day for children aged 1–3, 4–8 and 9–13 years, respectively. For children aged 14–18 years, ARs were assumed to be greater per kilogram body weight and the EAR was estimated to be 5.3 mg/kg body weight per day. Using reference body weights, EARs of 340 and 300 mg/day were derived for boys and girls, respectively. In the absence of information about the variation in requirement, a CV of 10 % was applied to all EAR values to derive the RDAs.

The SCF (1993) derived “quasi-PRIs” on the basis of body weights and assuming that requirements range from 7 mg/kg body weight per day (denoted slightly higher than the intake from breast milk) at 6–11 months to 4.2 mg/kg body weight per day (denoted slightly higher than the figure of 3.4 mg/kg body weight per day that is likely to be adequate in adults) at 15–17 years. An extra 30 % was added to allow for individual variations in growth. The SCF (1993) stressed the uncertainty around these values.

The Netherlands Food and Nutrition Council (1992) extrapolated Adequate Ranges of Intake for children from those for adults on the basis of body weight. For breast-fed infants a daily magnesium intake of 25–35 mg was estimated (Wacker and Parisi, 1968; Neville et al., 1984), and the Adequate Range of Intake for infants aged 6–12 months was set at 35–60 mg/day.

The UK COMA (DH, 1991) derived an EAR of 6 mg/kg body weight per day for infants aged 4–6 months on the basis of magnesium intake via breast milk reported to contain 28 mg/L (range 26–30 mg/L; DHSS (1980)). For children aged 6 months to 18 years, the EAR was assumed to be 4.5 mg/kg body weight per day, which was interpolated between the value for infants aged 4–6 months and the EAR on a body weight basis for adults (see Section 4.1). EARs were derived using reference body weights, and Reference Nutrient Intakes were set using CVs between 10 % and 16.5 % for the various age groups.

Table 3: Overview of Dietary Reference Values for magnesium for children

	D-A-CH (2015)	NCM (2014)	WHO/FAO (2004)	Afssa (2001)	IOM (1997)	SCF (1993)	NL (1992)	DH (1991)
Age (months)	4–<12	6–11	7–12	7–12	7–12	6–11	6–12	7–9
PRI (mg/day)	60	80	54 ^(a)	75	75 ^(b)	80 ^(a)	35–60 ^(c)	75
Age (years)								10–12
PRI (mg/day)								80
Age (years)	1–<4	1–<2	1–3	1–3	1–3	1–3	1–4	1–3
PRI (mg/day)	80	85	60 ^(a)	80	80	85 ^(a)	60–70 ^(c)	85
Age (years)	4–<7	2–5	4–6	4–6	4–8	4–6	4–7	4–6
PRI (mg/day)	120	120	76 ^(a)	130	130	120 ^(a)	90–100 ^(c)	120
Age (years)	7–<10	6–9	7–9	7–9		7–10	7–10	7–10
PRI (mg/day)	170	200	100 ^(a)	200		200 ^(a)	120–140 ^(c)	200
Age (years)	10–<13	10–13	10–18	10–12	9–13	11–14	10–13	11–14
PRI (mg/day)				280				
Boys	230	280	230 ^(a)		240	280 ^(a)	150–175 ^(c)	280
Girls	250	280	220 ^(a)		240	280 ^(a)	155–185 ^(c)	280
Age (years)	13–<15			13–15			13–16	
PRI (mg/day)								
Boys	310			410			220–255 ^(c)	
Girls	310			370			210–250 ^(c)	
Age (years)	15–<19	14–17		16–19	14–18	15–17	16–19	15–18
PRI (mg/day)								
Boys	400	350		410	410	300 ^(a)	275–325 ^(c)	300
Girls	350	280		370	360	300 ^(a)	225–275 ^(c)	300

NCM, Nordic Council of Ministers; NL, Netherlands Food and Nutrition Council.

(a): The uncertainty accompanying these values was expressed.

(b): AI.

(c): Adequate Range of Intake.

4.3. Pregnancy and lactation

The German-speaking countries (D-A-CH, 2015) stated that the fetus accumulates daily 5–7.5 mg of magnesium during the third trimester. It was, however, assumed that the RI for (young) non-pregnant women covers the requirement arising from this. During lactation, considering a mean magnesium concentration of breast milk of 31 mg/L and a milk secretion of 0.75 L/day, a daily magnesium loss of 24 mg via breast milk was assumed. Taking into account absorption efficiency, an additional magnesium intake of 80–90 mg/day was estimated to compensate for this loss.

For NNR 2012, it was considered that the RI for non-pregnant non-lactating women is sufficient to also cover the needs during pregnancy and lactation (Nordic Council of Ministers, 2014).

WHO/FAO (2004) considered that the fetus accumulates 8 mg and fetal adnexa accumulate 5 mg of magnesium during the whole pregnancy. Taking into account absorption efficiency, a total requirement of 26 mg over the whole pregnancy was calculated, which was assumed to be met by adaptation. Thus, the Recommended Nutrient Intake for pregnant women was the same as for non-pregnant women. During lactation, a daily magnesium loss of 25–28 mg via breast milk was assumed. An additional magnesium intake of 50–55 mg/day was estimated to cover this loss.

Afssa (2001) acknowledged that the requirement during pregnancy increases particularly during the third semester, owing to the transfer of magnesium to the fetus. Owing to the absence of compensatory mechanisms for this increased requirement, an additional intake of 40 mg/day was advised during pregnancy. For lactating women, an increase in intake of 30 mg/day was recommended, despite a decrease in urinary magnesium excretion and an increase in bone resorption that may contribute to meeting the increased magnesium requirement during lactation.

IOM (1997) considered that inconsistent findings on the effects of magnesium supplementation on pregnancy outcome make it difficult to determine if magnesium intakes greater than those recommended for non-pregnant women are beneficial. It was noted that there are no data indicating that magnesium is conserved during pregnancy or that intestinal absorption is increased. Thus, a factorial approach was used considering the gain in weight associated with pregnancy (increase in lean body mass of 6–9 kg with a midpoint of 7.5 kg (IOM, 1990), a magnesium concentration of lean body mass of 470 mg/kg (Widdowson and Dickerson, 1964) and an absorption efficiency of 40 % (Abrams et al., 1997)). A value of 33 mg/day was calculated and the additional requirement was set at 35 mg/day. For lactation, IOM (1997) considered that consistent evidence does not exist to support an increased requirement for dietary magnesium during lactation. It was stated that decreased urinary excretion of magnesium and increased bone resorption during lactation may provide the necessary magnesium for milk production. Therefore, the EAR and RDA were estimated to be the same as for non-lactating women of similar age and body weight.

The SCF (1993) stated that the Acceptable Range of Intakes for adults (i.e. 150–500 mg/day) also applies to pregnant and lactating women.

The Netherlands Food and Nutrition Council (1992) stated that balance studies in pregnant women have shown that a daily magnesium intake of 400 mg is not always sufficient to maintain balance and that the increased requirement for magnesium is probably greatest during the third trimester. An Adequate Range of Intake of 300–350 mg/day was set. For lactating women, an Adequate Range of Intake of 300–400 mg/day was derived.

The UK COMA (DH, 1991) considered that the fetus accumulates about 8 mg/day of magnesium and that there is a requirement of 10 mg/day for the accumulation of placenta and other tissues (Ziegler et al., 1976; Widdowson, 1980). However, it was considered that physiological adaptation during pregnancy and release from maternal stores ensures an adequate supply, and no additional intake was set. For lactating women, taking into account a magnesium concentration in breast milk of 28 mg/L (DHSS, 1980), assuming a magnesium secretion of 25 mg/day via milk and an absorption efficiency of 50 %, an additional intake of 50 mg/day was derived (Table 4).

Table 4: Overview of Dietary Reference Values for magnesium for pregnant and lactating women

	D-A-CH (2015)	NCM (2014)	WHO/FAO (2004)	Afssa (2001)	IOM (1997)	SCF (1993)	NL (1992)	DH (1991)
Pregnancy								
Additional intake (mg/day)	0	0	0	40	40	0	0–100	0
PRI (mg/day)	350 ^(a) /310 ^(b)	280	220	400 ^(c)	400 ^(a) 350 ^(d) 360 ^(e)	150–500 ^(f)	300–350 ^(g)	270
Lactation								
Additional intake (mg/day)	40 ^(a) /80 ^(b)	0	50	30	0	0	0–150	50
PRI (mg/day)	390	280	270	390	360 ^(a) 310 ^(d) 320 ^(e)	150–500 ^(f)	300–400 ^(g)	320

NCM, Nordic Council of Ministers; NL, Netherlands Food and Nutrition Council.

(a): < 19 years.

(b): ≥ 19 years.

(c): Women in the third trimester.

(d): 19–30 years.

(e): 31–50 years.

(f): Acceptable Range of Intakes.

(g): Adequate Range of Intake.

5. Criteria (endpoints) on which to base Dietary Reference Values

5.1. Biomarkers as indicators of magnesium requirement

As stated in Section 2.4, the Panel considers that there is no appropriate biomarker of magnesium intake or status that can be used for assessing magnesium requirement and for setting DRVs for magnesium.

5.2. Balance studies on magnesium

Balance studies are based on the assumption that a healthy subject on an adequate diet maintains an equilibrium or a null balance between nutrient intakes and nutrient losses: at this null balance, the intake matches the requirement determined by the given physiological state of the individual. When intakes exceed losses (positive balance), there is nutrient accretion that may be attributable to growth or to weight gain, anabolism or repletion of stores; when losses exceed intakes (negative balance), nutrient stores are progressively depleted resulting, in the long term, in clinical symptoms of deficiency. In addition to numerous methodological concerns about accuracy and precision in the determination of intakes and losses (Baer et al., 1999), the validity of balance studies for addressing requirements has been questioned: they might possibly reflect only adaptive changes before a new steady state is reached (Young, 1986), or they might reflect only the conditions for maintenance of nutrient stores and exchangeable body pools in the context of a given diet, and the relevance for health of the size of the pools still needs to be established for each nutrient (Mertz, 1987).

5.2.1. Balance studies in adults

Many studies have been performed to assess magnesium balance (Jones et al., 1967; Hunt and Schofield, 1969; Marxhall et al., 1976; Schwartz et al., 1978; Kelsay et al., 1979; Seelig, 1982; Kelsay and Prather, 1983; Mahalko et al., 1983; van Dokkum et al., 1983; Lakshmanan et al., 1984; Schwartz et al., 1984; Schwartz et al., 1986; Wisker et al., 1991; Spencer et al., 1994). Considering the balance studies in adults, which have an a priori sufficient adaptation period (see Appendix G), the Panel notes that many of these were conducted to assess interactions of some nutrients on magnesium absorption and balance, and that the diversity of background diets makes comparisons of the results of these balance studies difficult. The number of subjects included in the studies is generally small. Contrary to studies in children, most of the studies in adults did not express the results in relation to body weight. For most of the studies, the variability of intakes is limited (in the range 200–400 mg/day, with the exception of the study of Spencer et al. (1994)). For the only study reporting on individual values (Jones et al., 1967), the same approach as used by Hunt and Johnson (2006) (see next paragraph) resulted in a requirement of 219 mg/day or 4 mg/kg body weight per day. Recent studies in Japanese subjects reported zero balance for a magnesium intake of 4.1 mg/kg body weight per day (Nishimuta et al., 2006) and 4.2 mg/kg body weight per day (Nishimuta et al., 2012). The latter study was a compilation of 13 balance studies performed between 1986 and 2007 on a total of 131 female subjects. However, in the calculations, the adjustment to zero of the median values of several included studies where balances were positive hampers the interpretation of this result; moreover, adaptation periods in both studies (Nishimuta et al., 2006; Nishimuta et al., 2012) were very short (2–4 days). In the study by Nielsen and Milne (2004) in postmenopausal women, positive balances (1–26 mg/day) were observed for a magnesium intake between 310 and 334 mg/day.

Hunt and Johnson (2006) compiled the results of 27 balance studies conducted in a metabolic unit under well-controlled conditions. The 27 studies, in which the assessment of magnesium balance was not the primary study objective, were carried out between 1976 and 2000 on 243 apparently healthy subjects (150 women and 93 men, mean age 51 and 28 years, respectively), after excluding subjects who had insufficient (below the EAR) or excessive (above the 99th percentile) intakes of possibly interacting nutrients (calcium, copper, iron, phosphorus or zinc). The last 6–14 days of each equilibrating dietary period of at least 28 days were considered for the calculation of balances (difference between intakes and losses through faeces and urine), which resulted in 664 available data points. The majority of studies did not use magnesium supplements, whereas in some the basal diet

was supplemented with magnesium gluconate (or magnesium citrate dibasic in one study) to meet the RDA or a pre-defined experimental magnesium intake value. Null balance was achieved at a magnesium intake of 165 mg/day (95 % prediction interval = 113–237 mg/day; $Y = 19.8 + 0.880 M$, where Y refers to magnesium output and M refers to magnesium intake), corresponding to 2.36 mg/kg body weight per day (95 % prediction interval = 1.58–3.38 mg/kg body weight per day; $Y = 0.306 + 0.870 M$), or 0.075 mg/kcal per day (95 % prediction interval = 0.05–0.11 mg/kcal per day; $Y = 0.011 + 0.857 M$). Magnesium balance does not seem to be affected by age (subjects ranging in age from 20 to 80 years were included in the studies) or sex, suggesting that magnesium absorption does not change with age. From the characteristics of the statistical models, the authors concluded that there was strong homeostatic control of magnesium metabolism within the wide range of intakes observed in the studies (84–598 mg/day), especially with intakes below the null balance of 165 mg/day, with no suggestion of modifications of fractional magnesium absorption within this range.

Shils and Rude (1996) considered that magnesium balance studies were the most suitable basis for setting reference values for magnesium, provided careful consideration is given to the quality of the methodology used in the studies. Overall, the results of the studies summarised in Appendix G are inconsistent, and they therefore cannot be used to define the requirement for magnesium. On the other hand, considering the number of subjects of both sexes and the number of individual balance data, the large age range, the wide range of magnesium intake in the studies compiled, the comparability of experimental settings between the studies, especially the expression of results in relation to individual body weights, and the statistical analysis of the pooled data, the Panel considers that the balance studies compiled by Hunt and Johnson (2006) provide a stronger weight of evidence for adults than any of the other individual balance studies listed in Appendix G.

5.2.2. Balance studies and other indicators of requirement in children

There are some balance studies in children aged 7–9 years (Schofield and Morrell, 1960) and children aged 10–15 years (Schwartz et al., 1973; Greger et al., 1978; Greger et al., 1979; Andon et al., 1996; Abrams et al., 1997; Sojka et al., 1997) (see Appendix H). The Panel notes that most of these studies have limitations (small number of subjects, adaptation period short or absent) and are heterogeneous with respect to their primary objective (e.g. influence of another nutrient on magnesium balance) and background diet. The Panel notes that these studies have been used for setting DRVs for children (Section 4.2). The Panel also notes that requirements which may be derived from these balance studies with limitations are lower than average observed magnesium intakes in children (Section 3.2).

Magnesium accretion in bone is considered to be around 2.7 mg/day in infants aged 4–12 months and 3.1 and 4.2 mg/day in girls and boys, respectively, throughout childhood, with a peak rate of 8.4 mg/day in adolescence (Prentice and Bates, 1994). The Panel considers that this accretion rate constitutes only a small proportion and does not need to be considered in setting DRVs for magnesium for children.

Very few studies have investigated magnesium intake or status in relation to health outcomes in children (Huerta et al., 2005; Bo et al., 2007), and the Panel is unaware of studies in healthy children. The Panel considers that the available data on magnesium intake and health consequences in children cannot be used for setting DRVs for magnesium for children.

5.3. Indicators of magnesium requirement in pregnancy

Magnesium transfer to the fetus across the placenta occurs separately from that of calcium, through the paracellular route, and is driven by an electrochemical gradient; the existence of an active transport mechanism has still to be confirmed (Nandakumaran et al., 2002). The fetus accumulates magnesium, with a total content of around 0.6–0.8 g magnesium in mature fetuses weighing 3–4 kg, the percentage of magnesium in fetal fat-free mass being constant for fetuses weighing more than 2 kg, at around 0.26 mg/kg (Widdowson and Spray, 1951; Lentner, 1981). The placental magnesium content is low (around 36 mg; Challier et al. (1988)). The accretion of all these amounts would represent a daily net

magnesium transfer of around 2–3 mg. According to Ziegler et al. (1976), accretion varies from 1.8 mg/day at week 24–25 to 7.5 mg/day at week 36–37 and thereafter decreases to 5 mg/day at week 39–40; this gives an average daily accretion of 4.7 mg/day from week 24 to week 40.

Magnesium sulphate is promoted as an efficient treatment of pre-eclampsia and eclampsia (WHO, 2011), but the usefulness of magnesium supplementation during pregnancy for decreasing the risk of this adverse event is controversial because of the lack of good-quality data. A review of 10 randomised trials involving 9 090 women and their infants did not show an influence of magnesium supplementation on infant or maternal outcomes when they were studied as primary outcomes (Makrides et al., 2014).

A balance study in free-living subjects performed in the three trimesters of pregnancy in 10 women showed that a mean daily magnesium intake of 269 ± 55 mg led to a negative balance of -40 ± 50 mg (Ashe et al., 1979). According to Husain and Sibley (1993), this negative balance could be due to an unusually low fractional absorption of magnesium, as faecal loss represented around 80 % of the intake. Other limitations of the study are the small number of subjects, the use of self-selected diets and the absence of information on pre-pregnancy intake, whereas a strength is the determination of four to six 7-day balances for each woman (two per trimester). Ashe et al. (1979) stated that the high within- and between-subject variability in magnesium intake might have obscured physiological adaptations occurring in the later part of pregnancy.

The Panel concludes that infant or maternal clinical outcomes during pregnancy cannot be used to assess magnesium requirements during this phase. On the other hand, the available evidence indicates that there is only a small additional requirement during pregnancy which may be met by adaptive metabolic changes.

5.4. Indicators of magnesium requirement in lactation

According to Dorea (2000), concentrations of magnesium reported for breast milk vary over a wide range (15–64 mg/L), with a median value of 31 mg/L and 75 % of reported mean concentrations being below 35 mg/L (see Section 2.3.5.5). Dengel et al. (1994) compared six lactating and six post partum non-lactating women (75 ± 5 and 61 ± 5 days post partum, respectively) with seven never-pregnant women who received a constant diet providing 218 mg magnesium/day for 20 days. After an equilibration period of 5 days, urine and faeces were collected for the next 15 days. Comparing lactating women with never-pregnant women, the authors observed that the export in milk of around 25 mg/day was compensated for by a reduction of 33 mg/day in urinary magnesium excretion. The Panel considers that there are adaptive mechanisms so that there may be no need to compensate for the amount of magnesium secreted in breast milk during lactation.

5.5. Magnesium intake and health consequences

A comprehensive literature search covering the period from 1990 to October 2011 was performed as preparatory work to the present Opinion, focusing on original studies reporting on quantitative relationships between intake and status, status and health or intake and health (Brown et al., 2012). Overall, the preparatory report concluded that high-quality data for health outcomes on which to derive DRVs for magnesium are limited. The literature search was continuously updated until adoption of this Opinion.

Many clinical conditions have been studied in relation to magnesium intake/status that consider the therapeutic potential of magnesium (such as in migraine headaches, neuromuscular conditions such as restless leg syndrome, or clinical depression) or its potential role on the basis of mechanistic considerations, such as for the immune system (Wu and Veillette, 2011). The analysis presented in this section is restricted to the conditions relevant for the general healthy population, where a sufficient body of evidence exists and quantitative data on magnesium intake are available (studies only reporting on serum magnesium concentration are not considered in this section).

5.5.1. Cardiovascular disease-related outcomes

5.5.1.1. Blood pressure

Previous systematic reviews and meta-analyses on studies investigating the effect of magnesium supplementation on systolic (SBP) and diastolic blood pressure (DBP) have shown inconclusive results. Several of these reviews included hypertensive subjects, and information on dietary magnesium intake was not generally available (Burgess et al., 1999; Jee et al., 2002; Dickinson et al., 2006; Kass et al., 2012). From the compilation of 30 observational studies (mainly cross-sectional), Mizushima et al. (1998) concluded that there may be an inverse relationship between magnesium intake and SBP and DBP, although quantitative analysis was not possible because of heterogeneity and various methodological limitations. In a recent cross-over study lasting 8 weeks, with a 4-week wash-out period in between, supplementation of magnesium (368 mg/day) to 14 healthy normotensive young men did not affect their SBP or DBP (Cosaro et al., 2014).

5.5.1.2. Cardiovascular events

The meta-analysis by Qu et al. (2013a) included 13 prospective cohort studies reporting on dietary magnesium (477 680 participants and over 14 900 cardiovascular events) and showed a significant inverse association between magnesium intake and risk of cardiovascular disease (CVD) events comprising stroke, coronary heart disease and CVD death (relative risk (RR) = 0.85, 95 % confidence interval (CI) = 0.78–0.92, $I^2 = 39$ %, comparing the highest and the lowest category of magnesium intake). Dose-response analyses showed evidence of a non-linear association, with the greatest reduction occurring for a magnesium intake between 150 and 400 mg/day, although it is unclear if supplement use was always considered.

The meta-analysis by Del Gobbo et al. (2013) included nine prospective studies providing estimates of dietary magnesium, mostly from validated food frequency questionnaires, with a median intake across studies of 289 mg/day, and incident CVD (including 7 889 CVD events, 4 319 events of ischaemic heart disease and 1 158 fatal ischaemic heart disease events). Only two of the nine studies described the use of magnesium supplements, and seven of the nine studies were also considered by Qu et al. (2013a). Using increments of 200 mg/day in dietary magnesium, dietary intake was not associated with total CVD. The authors found a significant non-linear association with fatal ischaemic heart disease; in comparison with lower intakes, a 27 % lower risk of fatal ischaemic heart disease was observed up to a magnesium intake of about 250 mg/day (RR = 0.73, 95 % CI = 0.62–0.86).

Combining six prospective cohort studies (including four already included in the meta-analyses of Qu et al. (2013a) and Del Gobbo et al. (2013)), the meta-analysis by Xu et al. (2013) did not find a significant association between magnesium intake and total CVD mortality; however, a subgroup analysis suggested an inverse association in women, leading the authors to conclude that sex might be one of the major sources of heterogeneity between studies. This meta-analysis included only studies providing adjusted risk estimates, but also included two studies focusing on magnesium intake from water (and using this intake for comparisons).

The Panel notes the discrepancies between these meta-analyses, suggesting that inclusion of non-adjusted results might confound the association of magnesium intake and CVD events.

In the Nurses' Health Study, the relationship between dietary magnesium (including from supplements) and the risk of coronary heart disease after a median follow-up of 28 years was investigated (Chiuve et al., 2013). After controlling for classical coronary heart disease risk factors, higher magnesium intake was not associated with overall coronary heart disease risk; however, the authors observed a lower risk of fatal coronary heart disease (RR = 0.61, 95 % CI = 0.45–0.84) comparing the highest quintile (dietary intake > 342 mg/day) to the lowest quintile (< 246 mg/day). A cross-sectional study in 2 695 men and women of the Framingham cohort showed an inverse association of total (i.e. dietary and supplemental) magnesium intake with calcification of the coronary artery, with each 50-mg/day increment in magnesium intake resulting in 22 % less calcification

($p < 0.001$), whereas total magnesium intake was not associated with calcification of the abdominal aorta (Hruby et al., 2014).

5.5.1.3. Stroke

Nie et al. (2013) performed a meta-analysis on the relationship between magnesium intake and stroke, including eight prospective cohort studies (8 367 strokes in 304 551 participants). The weighted average magnesium intake was 306 mg/day (range 228–471 mg/day). There was an inverse association between magnesium intake and incidence of total stroke (RR = 0.89, 95 % CI = 0.82–0.97, $I^2 = 0$ %); the dose–response analysis showed a small borderline significant inverse association between magnesium intake per 100-mg/day increment and total stroke risk (RR = 0.98, 95 % CI = 0.95–1.00, $I^2 = 33$ %), whereas subgroup analysis showed a significantly lower risk of ischaemic stroke when comparing the highest intake with the lowest intake (RR = 0.88, 95 % CI = 0.80–0.98, p for heterogeneity = 0.509). These results are similar to those of Larsson et al. (2012), whose meta-analysis included seven prospective studies (6 477 strokes among 241 378 participants; only one out of seven studies showed a significant reduction in stroke incidence) that were also included in the meta-analysis by Nie et al. (2013). For every 100-mg/day increment in magnesium intake, the risk of total stroke slightly decreased (RR = 0.92, 95 % CI = 0.88–0.99, $I^2 = 0$ %). An inverse association between magnesium intake and stroke risk was also observed in the Dutch cohorts ($n = 36$ 094, 631 strokes) of the European Prospective Investigation into Cancer and Nutrition study (Sluijs et al., 2014). Total magnesium intake (i.e. from diet and supplements) for the lowest and the highest quartile was ≤ 285 mg/day and ≥ 398 mg/day, respectively. Per 100-mg/day increment in total magnesium intake, stroke risk decreased by 22 % (hazard ratio = 0.78, 95 % CI = 0.65–0.93).

5.5.1.4. Arrhythmia

Although magnesium has been suggested for the therapy of arrhythmia, few studies have investigated the relationship between magnesium intake and heart rhythm changes in apparently healthy populations. Nielsen et al. (2007) submitted 14 healthy postmenopausal women to a magnesium depletion diet providing 100 mg/8.4 MJ (2 000 kcal) per day; the depletion period was planned to have a duration of 78 days. Five women developed heart rhythm alterations which required magnesium repletion earlier than planned (after 42–64 days instead of after 78 days). This study suggests that a daily magnesium intake of 100 mg/8.4 MJ may be inadequate. In white and African American men and women in the prospective Atherosclerosis Risk in Communities study, no association was observed between dietary magnesium intake and risk of atrial fibrillation (Misialek et al., 2013).

5.5.1.5. Conclusions on cardiovascular disease-related outcomes

The Panel notes that the association between magnesium intake and CVD-related outcomes may be confounded by dietary fibre intake and other dietary factors. For example, in the meta-analysis of 19 studies by Qu et al. (2013a), only four of the included studies have adjusted for dietary fibre and only three for potassium intake. Del Gobbo et al. (2013) reported that about half of the studies included in their meta-analysis were adjusted for both sociodemographic and lifestyle variables including age, sex, ethnicity, body mass index (BMI), waist circumference, smoking, alcohol consumption and physical activity. Therefore, for all these studies, it is difficult to unravel the effect of magnesium per se from the effect of foods rich in magnesium or the effect of the total diets associated with consumption of these foods.

The Panel considers that data on magnesium intake and CVD-related outcomes cannot be used for setting DRVs for magnesium.

5.5.2. Metabolic syndrome

Some studies have investigated the relationship between magnesium intake and the risk of metabolic syndrome. Combining eight cross-sectional and two prospective cohort studies (30 092 participants, eight studies with healthy subjects and two studies including patients with diabetes mellitus type 2 and recipients of living-donor kidney transplant), Ju et al. (2014) showed that every 150-mg/day increment

in magnesium intake was inversely associated with risk of metabolic syndrome (pooled RR = 0.88, 95 % CI = 0.84–0.93, $I^2 = 36$ %). The meta-analysis of Dibaba et al. (2014) on six cross-sectional studies (6 311 cases of metabolic syndrome among 24 473 individuals), of which all but one were also included in the meta-analysis of Ju et al. (2014), also concluded that there was an inverse association between magnesium intake and the risk of metabolic syndrome.

The Panel considers that data on magnesium intake and metabolic syndrome cannot be used for setting DRVs for magnesium.

5.5.3. Diabetes mellitus type 2

In the meta-analysis of Larsson and Wolk (2007) of seven prospective cohort studies (10 912 incident cases among 286 668 participants), the relative risk of diabetes mellitus type 2 for a 100-mg/day increase in magnesium intake was 0.85 (95 % CI = 0.79–0.92). In the dose–response analysis, studies were combined reporting associations between diabetes risk and magnesium intake (assessed continuously or categorically).

The meta-analysis by Dong et al. (2011) with 13 prospective cohort studies (24 516 incident cases for 536 318 participants, including the studies analysed by Larsson and Wolk (2007)) found a relative risk of 0.86 (95 % CI = 0.82–0.89) for each 100-mg/day increment in magnesium intake. In this meta-analysis, the relative risk was not significantly modified when considering only the studies where adjustments were made for dietary fibre intake. In addition, the observed inverse association remained in a subgroup analysis among studies of individuals with an average BMI $\geq 25 \text{ kg} \times \text{m}^{-2}$, but no association was observed among those with a BMI $< 25 \text{ kg} \times \text{m}^{-2}$. This finding suggests that the evidence for an inverse association may not be consistent and may concern overweight/obese individuals rather than normal-weight individuals, which make up the target population for DRVs. However, in the very large cohorts of the Nurses' Health Study and the Health Professionals Follow-up Study (included in the meta-analysis), no significant interaction was observed between magnesium intake and BMI, and the risk reduction remained significant in stratified analysis by BMI (≤ 27 and $> 27 \text{ kg} \times \text{m}^{-2}$) (Lopez-Ridaura et al., 2004). The Panel notes that the association between magnesium intake and diabetes mellitus type 2 may be confounded by dietary fibre intake and other dietary factors and that several observational studies did not adjust for this.

In the most recent study (Weng et al., 2012), not included in the aforementioned meta-analysis, 1 604 Taiwanese men and women were followed up for a period of 4.6 years. Risk of diabetes mellitus type 2 was inversely associated with magnesium intake (HR = 2.61, 95 % CI = 1.42–4.79, comparing the lowest quintile (median magnesium intake 212 mg/day) with the highest quintile (median intake 406 mg/day, reference quintile), p for trend = 0.001).

Details on magnesium intake and risk estimates for the individual prospective studies included in the meta-analysis by Dong et al. (2011) and for the study by Weng et al. (2012) are given in Appendix I.

Supplementation studies in subjects with diabetes mellitus type 1 or type 2 or in overweight individuals with insulin resistance show inconsistent results with respect to improvement of insulin sensitivity and glycaemic control (Sales and Pedrosa Lde, 2006; Martini et al., 2010; Volpe, 2013).

The Panel considers that there is evidence for an inverse association between magnesium intake and the risk of diabetes mellitus type 2. The Panel notes that there is insufficient evidence for a dose–response relationship between magnesium intake and type 2 diabetes risk and considers that data on magnesium intake and diabetes mellitus type 2 cannot be used for setting DRVs for magnesium.

5.5.4. Cancer

In the report by WCRF/AICR (2007), magnesium was not considered as such, but some subsequent studies point to a possible association between magnesium intake and colorectal cancer risk.

The meta-analysis of Chen et al. (2012) included eight prospective studies with 338 979 participants and 8 000 colorectal cancer cases. The summary relative risk for the highest versus the lowest category of magnesium intake for colorectal cancer was 0.89 (95 % CI = 0.79–1.00, $I^2 = 0$ %). In dose–response analyses, every 50-mg/day increment in magnesium intake was associated with a 5 % reduced risk of colorectal cancer (RR = 0.95, 95 % CI = 0.89–1.00, $I^2 = 49$ %). Similar results were obtained in the meta-analysis of Qu et al. (2013b) of seven prospective cohort studies (333 510 participants and 7 435 cases), all of which were also considered by Chen et al. (2012). Qu et al. (2013b) observed a non-linear dose–response relationship between dietary magnesium and the risk of colorectal cancer (for every 100-mg/day increment in magnesium intake, RR = 0.82, 95 % CI = 0.64–1.00, $I^2 = 63$ %), with the greatest reduction of risk for an intake between 200 and 270 mg/day, but little evidence of a further reduction with higher intakes.

The Panel considers that the available information on the relationship between dietary magnesium and colorectal cancer risk is insufficient to provide a basis for setting DRVs for magnesium.

5.5.5. Bone health-related outcomes

Magnesium has an impact on bone health through its role in the structure of hydroxyapatite crystals in bone. Some studies of different design (cross-sectional and prospective observational studies, intervention studies using magnesium supplementation) reported on various associations of magnesium intake with bone mineral density (BMD) or bone mineral content (BMC) (Tucker et al., 1999; Ryder et al., 2005; Carpenter et al., 2006; Farrell et al., 2009). Carpenter et al. (2006) enrolled 8- to 14-year-old girls with a dietary magnesium intake below 220 mg/day; supplementation with 300 mg/day for one year significantly increased serum magnesium concentration and BMC of the hip by about 3 %, but not of the lumbar spine, compared with placebo. There was no difference in BMD between the treatment and placebo groups. In 73 684 postmenopausal women enrolled in the prospective Women’s Health Initiative Observational Study (Orchard et al., 2014), baseline hip BMD was 3 % higher ($p < 0.001$) and whole-body BMD was 2 % higher ($p < 0.001$) in women who consumed > 423 mg magnesium/day than in those who consumed < 207 mg/day. However, the incidence and relative risks of hip and total fractures occurring during an average of 7.6 years of follow-up did not differ across quintiles of magnesium intake. In contrast, the risk of lower arm or wrist fractures increased significantly with higher magnesium intakes. As the women with the highest magnesium intake were also more physically active and at increased risk of falls, the authors concluded that the association between magnesium intake and fractures may possibly be related to more physical activity and falls.

In their literature search, Brown et al. (2012) retrieved two studies which reported on the influence of magnesium on markers of bone formation and bone resorption, one of which was an uncontrolled study (Fatemi et al., 1991). Doyle et al. (1999) conducted a randomised cross-over study in 26 young women, which compared a usual dietary magnesium intake (about 275 mg/day) for four weeks with a usual dietary intake supplemented with about 250 mg magnesium/day for four weeks. There were no significant differences in biomarkers of bone formation and resorption between the two study periods.

The Panel notes that, although the role of magnesium in bone structure and physiology is well established, there are few quantitative data for using this relationship for setting DRVs for magnesium.

6. Data on which to base Dietary Reference Values

The Panel considers that there is no appropriate biomarker of magnesium intake or status that can be used for assessing magnesium requirement and for setting DRVs for magnesium (see Section 5.1).

6.1. Adults

The Panel notes that a recent pooled analysis of well-controlled balance studies in adults suggests that zero magnesium balance may occur at a magnesium intake of 165 mg/day (95 % prediction interval based on a linear mixed-effect model: 113–237 mg/day) (Section 5.2.1). The Panel, bearing in mind that balance studies might also reflect adaptive changes before a new steady state is reached, evaluated

the evidence from balance studies in combination with the findings of large-scale and long-term prospective observational studies. Several of these studies point to an inverse relationship between magnesium intake and the risk of diabetes mellitus type 2 at daily intakes ranging between 244 and 773 mg/day (medians of highest quintiles), compared with daily intakes ranging between 115 and 270 mg/day (medians of lowest quintiles). The Panel notes, however, that there is insufficient evidence of a dose–response relationship between magnesium intake and the risk of diabetes mellitus type 2 in the general healthy population and that the evidence cannot be used to identify a certain magnesium intake above which the risk of diabetes mellitus type 2 is not further reduced.

Considering all of the evidence available, the Panel decided to set AIs based on observed intakes in several EU countries. The range of average intakes for nine European countries is 317–439 mg/day (midpoint 378 mg/day) for men and 254–357 mg/day (midpoint 306 mg/day) for women aged 18 to < 65 years (see Appendices C and D). For older adults (65 to < 75 years), the ranges are 312–407 mg/day (midpoint 360 mg/day) for men and 241–343 mg/day (midpoint 292 mg/day) for women. For adults above 75 years of age, the ranges are 264–388 mg/day (midpoint 326 mg/day) for men and 232–347 mg/day (midpoint 290 mg/day) for women. The Panel notes that midpoints of ranges for intake estimates in these age and sex groups are in good agreement with medians for the sex and age groups of the average intakes estimated per survey.

The Panel notes that there is at present insufficient evidence for considering different DRVs according to age in adults and decided to merge the ranges for all men above 18 years (observed mean magnesium intakes of 264–439 mg/day), for which the midpoint is 352 mg/day. Similarly, for women, the merged range for all women above 18 years is 232–357 mg/day, with a midpoint of 295 mg/day. The median of average intakes of women of all ages is 298 mg/day, and the median of average intakes of men of all ages is 341 mg/day.

Considering the rather large differences in magnesium intakes between men and women, the Panel proposes to set AIs according to sex. The Panel notes that the expression of results on the basis of energy intake would correspond to the involvement of magnesium in many biochemical processes (Section 2.2.1) and would also allow the rather large differences in energy intake in adults to be taken into account. For these reasons, the Panel decided to report, in Appendices C and D, the results also in mg/MJ and notes that intakes per unit energy are similar between men and women (see also Section 3.2). However, the Panel considers that the use of DRVs for energy for setting DRVs for magnesium would require additional assumptions (e.g. selection of a specific physical activity level), which would lead to further uncertainties. Thus, for men, considering the distribution of the observed average intakes, the Panel proposes an AI of 350 mg/day. For women, on the same basis, the Panel proposes an AI of 300 mg/day.

The Panel considers that these AIs apply to all adults, including older adults.

6.2. Infants aged 7–11 months

The Panel notes that, in breast-fed infants aged 0–6 months, magnesium intake is estimated to be around 25 mg/day (Section 2.3.5.5). Using isometric scaling as the most conservative extrapolation method, which is justified by bone magnesium accretion, to extrapolate to the magnesium intake of infants aged 7–11 months results in an estimated magnesium intake of 35 mg/day in older infants. This is calculated using the formula below and rounding to the nearest unit. Averages of the median weight-for-age of male and female infants aged 3 months (6.1 kg) and 9 months (8.6 kg) according to the WHO Growth Standards (WHO Multicentre Growth Reference Study Group, 2006) are used for the calculation.

$$\text{Magnesium intake of infants aged 7–11 months} = \text{magnesium intake of infants aged 0–6 months} \times (\text{body weight of infants aged 9 months} / \text{body weight of infants aged 3 months})$$

The SCF (1993) proposed a guidance value of 80 mg/day on the basis of intakes considered appropriate for the majority of infants aged 6 to < 12 months, amounting to 3.5–7 mg/kg body weight per day, in line with the results of balance studies in older children.

The Panel notes that the mean observed intakes in four EU countries for which data are available are in the range 72–120 mg/day (Appendices C and D). These estimates include the consumption of food products for the young population and thus of foods fortified with magnesium in accordance with current EU regulations (see Section 3.1).

Therefore, a potential range for DRVs for magnesium would be 35 to 120 mg/day (midpoint 78 mg/day). In the absence of other evidence and in line with the proposal by the SCF (1993), the Panel decided to set an AI for infants aged 7–11 months of 80 mg/day.

6.3. Children

In the absence of well-controlled balance studies in children and of other evidence that may be used for deriving a requirement for magnesium in children, the Panel decided to set AIs based on observed intakes in EU countries.

As for adults (Section 6.2), the Panel considers that the use of DRVs for energy for setting DRVs for magnesium would require additional assumptions (e.g. selection of a specific physical activity level), which would lead to further uncertainties. Thus, the Panel decided to set DRVs for magnesium for children in mg/day.

In children aged 1 to < 3 years, mean observed magnesium intake from five surveys in four EU countries ranges from 162 to 188 mg/day (midpoint 175 mg/day) in boys and from 153 to 174 mg/day (midpoint 164 mg/day) in girls (Appendices C and D). For boys and girls aged 1 to < 3 years, considering the absence of a strong basis for a distinct value according to sex and the distribution of the observed mean intakes, the Panel selects the midpoint of average intakes and sets an AI of 170 mg/day for boys and girls.

In children aged 3 to < 10 years, mean observed magnesium intake from seven surveys in six EU countries ranges from 202 to 281 mg/day (midpoint 242 mg/day) in boys and from 184 to 259 mg/day (midpoint 222 mg/day) in girls (Appendices C and D). For boys and girls aged 3 to < 10 years, on the same basis as for children aged 1 to < 3 years, considering the distribution of the observed mean intakes, the Panel selects the midpoint of average intakes and sets an AI of 230 mg/day for boys and girls.

In children aged 10 to < 18 years, mean observed magnesium intake from seven surveys in seven EU countries ranges from 257 to 344 mg/day (midpoint 301 mg/day) in boys and from 213 to 384 mg/day (midpoint 299 mg/day) in girls (Appendices C and D). However, the Panel notes that the data provided for Latvia include pregnant girls younger than 18 years and that intakes are rather high compared with other datasets; excluding Latvia provides a narrower range of intakes of 213–292 mg/day (midpoint 253 mg/day). Considering the rather large differences in magnesium intakes between boys and girls aged 10 to < 18 years, the Panel proposes to set AIs according to sex. For boys aged 10 to < 18 years, considering the distribution of the observed average intakes, the Panel selects the midpoint of average intakes and sets an AI of 300 mg/day. For girls aged 10 to < 18 years, considering the distribution of the observed average intakes, the Panel selects the midpoint of average intakes in non-pregnant girls and sets an AI of 250 mg/day.

6.4. Pregnancy

Considering that pregnancy induces only a small increase in magnesium requirement (see Section 5.3), which is probably covered by adaptive physiological mechanisms and increases in energy intake in pregnancy (EFSA NDA Panel, 2013), the Panel considers that the AI for non-pregnant women also applies to pregnant women.

6.5. Lactation

About 25 mg/day is secreted with exclusive breastfeeding during the first six months after birth (see Section 2.3.5.5).

The Panel notes the possibility of adaptive processes in magnesium metabolism, at the level of both absorption and elimination (see Section 2), and considers that an additional dietary intake may not be needed during the lactation period. The study by Dengel et al. (1994) (see Section 5.4) supports this approach.

The Panel concludes that the AI for non-pregnant non-lactating women also applies to lactating women.

CONCLUSIONS

The Panel concludes that ARs and PRIs for magnesium cannot be derived for adults, infants or children, and proposes AIs based on observed intakes (Table 5). For children and adults, this approach considers the range of average magnesium intakes estimated from dietary surveys in nine EU countries. For infants aged 7–11 months, the Panel proposes AIs after consideration of observed intakes, estimated intakes in fully breast-fed infants and upwards extrapolation by isometric scaling. The AI set for pregnant and lactating women is the same as for non-pregnant non-lactating women.

Table 5: Summary of Adequate Intakes for magnesium

Age	Adequate Intake (mg/day)	
	Males	Females
7–11 months	80	80
1–< 3 years	170	170
3–< 10 years	230	230
10–< 18 years	300	250
≥ 18 years ^(a)	350	300

(a): Including pregnant and lactating women.

RECOMMENDATIONS FOR RESEARCH

The Panel recommends that research is needed to characterise systematically:

- the functional and homeostatic responses to a range of exposures to magnesium with a view to identifying and validating markers of marginally adequate and excessive intakes of magnesium and of chronic and acute magnesium status. Such work might include, for example, investigating the value of urinary excretion of magnesium, the magnesium tolerance test and the content of magnesium in blood cells and platelets;
- the nature of possible pathogenic bases for the association of low magnesium status with impaired substrate (carbohydrate and lipid) metabolism, and sequelae of the metabolic syndrome including diabetes mellitus.

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APPENDICES

Appendix A. Magnesium concentration in human milk of mothers of term infants

Reference	Number of women (number of samples)	Country	Stage of lactation	Magnesium concentration (mg/L)		
				Mean \pm SD	Median	Range
Bauer and Gerss (2011)	10	Germany	1–8 weeks	31.6 \pm 4.86		
Bjorklund et al. (2012)	60	Sweden	14–21 days	28 \pm 4.8	28	21–43
Bocca et al. (2000)	60 (60)	Italy	Not reported	23.0 \pm 0.51		
Doybak et al. (1999)	35	Turkey	1–4 months (28–123 days)	1 st month: 28 \pm 7 4 th month: 31 \pm 8		
Friel et al. (1999)	19 (136) (17) (16) (16) (15) (15) (15) (15) (15) (12)	Canada	2 or 3 days to 3 months	Week 1: 30.41 \pm 4.74 Week 2: 26.69 \pm 3.98 Week 3: 26.25 \pm 4.40 Week 4: 26.73 \pm 4.71 Week 5: 28.33 \pm 5.59 Week 6: 29.20 \pm 5.02 Week 7: 31.47 \pm 5.76 Week 8: 33.20 \pm 5.24 Week 12: 34.58 \pm 6.02		26–35
Hunt et al. (2005)	45	USA	> 10 days to 4 months	Month 1: 28.6 \pm 2.2 Month 4: 33.0 \pm 2.2		
Rakicioglu et al. (2006)	21	Turkey	2–5 months	During Ramadan (2 nd week): 29 \pm 5 2 weeks after the end of Ramadan: 33 \pm 5		
Sievers et al. (2000)	14 infants	Germany	Infant age median 3.6 weeks (range 2.6–4.7)		28.6	21.2–44
Vitolo et al. (2004)	90	Brazil	30–90 days	Low socio-economic adolescents (n = 31): 25.8 \pm 4.4 Low socio-economic women (n = 30): 28.2 \pm 5.6 High socio-economic women (n = 29): 27.0 \pm 5.6		

Reference	Number of women (number of samples)	Country	Stage of lactation	Magnesium concentration (mg/L)		
				Mean \pm SD	Median	Range
Witczak and Jarnuszevska (2011)	(9)	Poland	5–6 months	40		
Yamawaki et al. (2005)	(1170) Summer: (577) Winter: (593)	Japan	1–365 days	<u>Mean total:</u> 27 ± 9 <u>By season:</u> Summer: 26 ± 9 Winter: 27 ± 9 <u>By stage of lactation:</u> Day 1–5: 32 ± 5 Day 6–10: 30 ± 9 Day 11–20: 29 ± 6 Day 21–89: 25 ± 7 Day 90–180: 27 ± 11 Day 181–365: 33 ± 7		

This table lists studies not yet considered in the review by Dorea (2000).

Appendix B. Dietary surveys in the EFSA Comprehensive European Food Consumption Database included in the nutrient intake calculation and number of subjects in the different age classes

Country	Dietary survey	Year	Method	Days	Age (years)	Number of subjects						
						Infants < 1 year	Children 1–< 3 years	Children 3–< 10 years	Children 10–< 18 years	Adults 18–< 65 years	Adults 65–< 75 years	Adults ≥ 75 years
Finland/1	DIPP	2000–2010	Dietary record	3	< 1–6	499	500	750				
Finland/2	NWSSP	2007–2008	48-hour dietary recall ^(a)	2 × 2 ^(a)	13–15				306			
Finland/3	FINDIET2012	2012	48-hour dietary recall ^(a)	2 ^(a)	25–74					1 295	413	
France	INCA2	2006–2007	Dietary record	7	3–79			482	973	2 276	264	84
Germany/1	EsKiMo	2006	Dietary record	3	6–11			835	393			
Germany/2	VELS	2001–2002	Dietary record	6	< 1–4	159	347	299				
Ireland	NANS	2008–2010	Dietary record	4	18–90					1 274	149	77
Italy	INRAN-SCAI 2005–06	2005–2006	Dietary record	3	< 1–98	16 ^(b)	36 ^(b)	193	247	2 313	290	228
Latvia	FC_PREGNANTWOMEN	2011	24-hour dietary recall	2	15–45				12 ^(b)	991 ^(c)		
Netherlands	DNFCS	2007–2010	24-hour dietary recall	2	7–69			447	1 142	2 057	173	
Sweden	RISKMATEN	2010–2011	Dietary record (web) ^(d)	4	18–80					1 430	295	72
United Kingdom/1	DNSIYC-2011	2011	Dietary record	4	0.3–1.5	1 369	1 314					
United Kingdom/2	NDNS Rolling Programme (Years 1–3)	2008–2011	Dietary record	4	1–94		185	651	666	1 266	166	139

DIPP, Type 1 Diabetes Prediction and Prevention survey; DNFCS, Dutch National Food Consumption Survey; DNSIYC, Diet and Nutrition Survey of Infants and Young Children; EsKiMo, Ernährungsstudie als KIGGS-Modul; FINDIET, the national dietary survey of Finland; INCA, Étude Individuelle Nationale des Consommations Alimentaires; INRAN-SCAI, Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione – Studio sui Consumi Alimentari in Italia; FC_PREGNANTWOMEN, food consumption of pregnant women in Latvia; NANS, National Adult Nutrition Survey; NDNS, National Diet and Nutrition Survey; NWSSP, Nutrition and Wellbeing of Secondary School Pupils; VELS, Verzehrsstudie zur Ermittlung der Lebensmittelaufnahme von Säuglingen und Kleinkindern für die Abschätzung eines akuten Toxizitätsrisikos durch Rückstände von Pflanzenschutzmitteln.

(a): A 48-hour dietary recall comprises two consecutive days.

(b): 5th or 95th percentile intakes calculated from fewer than 60 subjects require cautious interpretation, as the results may not be statistically robust (EFSA, 2011b) and, therefore, for these dietary surveys/age classes, the 5th and 95th percentile estimates will not be presented in the intake results.

(c): One subject was excluded from the dataset because only one 24-hour dietary recall day was available, i.e. final n = 990.

(d): The Swedish dietary records were introduced through the internet.

Appendix C. Magnesium intake in males in different surveys according to age classes and country

Age	Country	Survey	n ^(a)	Intake expressed in mg/day				n ^(a)	Intake expressed in mg/MJ			
				Average	Median	P5	P95		Average	Median	P5	P95
< 1 year ^(b)	Finland	DIPP_2001_2009	247	76	80	15	131	245	42	38	26	68
	Germany	VELS	84	111	103	60	173	84	34	34	21	48
	Italy	INRAN_SCAI_2005_06	9	76	56	(c)	(c)	9	25	24	(c)	(c)
	United Kingdom	DNSIYC_2011	699	120	117	63	186	699	35	35	22	48
1 to < 3 years	Finland	DIPP_2001_2009	245	162	160	91	236	245	45	44	29	59
	Germany	VELS	174	169	167	107	250	174	36	36	26	48
	Italy	INRAN_SCAI_2005_06	20	173	170	(c)	(c)	20	35	36	(c)	(c)
	United Kingdom	DNSIYC_2011	663	168	164	97	247	663	40	39	28	53
	United Kingdom	NDNS RollingProgramme Years 1–3	107	188	182	129	268	107	39	37	29	54
3 to < 10 years	Finland	DIPP_2001_2009	381	245	241	169	332	381	42	42	32	53
	France	INCA2	239	215	205	118	329	239	34	33	25	48
	Germany	EsKiMo	426	281	272	181	398	426	37	36	27	49
	Germany	VELS	146	202	190	125	307	146	36	35	26	48
	Italy	INRAN_SCAI_2005_06	94	249	238	161	366	94	34	32	24	49
	Netherlands	DNFCS 2007–2010	231	248	241	151	371	231	29	29	19	41
	United Kingdom	NDNS RollingProgramme Years 1–3	326	225	218	139	326	326	36	35	26	49
10 to < 18 years	Finland	NWSSP07_08	136	344	327	201	501	136	43	43	28	59
	France	INCA2	449	257	248	152	399	449	33	32	24	44
	Germany	EsKiMo	197	292	282	180	439	197	36	36	26	49
	Italy	INRAN_SCAI_2005_06	108	309	298	189	461	108	32	30	23	44
	Netherlands	DNFCS 2007–2010	566	298	284	168	473	566	28	27	18	40
	United Kingdom	NDNS RollingProgramme Years 1–3	340	259	253	153	405	340	32	31	23	45
18 to < 65 years	Finland	FINDIET2012	585	402	391	227	602	585	44	43	31	60
	France	INCA2	936	317	305	176	487	936	36	35	25	51
	Ireland	NANS_2012	634	367	356	193	577	634	37	36	25	52
	Italy	INRAN_SCAI_2005_06	1 068	357	347	214	529	1 068	40	38	27	59
	Netherlands	DNFCS 2007–2010	1 023	388	372	218	597	1 023	35	34	22	51
	Sweden	Riksmaten 2010	623	439	425	211	704	623	45	43	30	65
	United Kingdom	NDNS RollingProgramme Years 1–3	560	321	312	170	511	560	37	36	24	52

Age	Country	Survey	n ^(a)	Intake expressed in mg/day				n ^(a)	Intake expressed in mg/MJ			
				Average	Median	P5	P95		Average	Median	P5	P95
65 to < 75 years	Finland	FINDIET2012	210	360	351	202	544	210	45	44	30	62
	France	INCA2	111	312	309	175	465	111	36	35	27	48
	Ireland	NANS_2012	72	331	328	145	497	72	38	37	23	56
	Italy	INRAN_SCAI_2005_06	133	357	351	190	514	133	41	39	30	59
	Netherlands	DNFCS 2007–2010	91	342	336	214	488	91	38	37	26	53
	Sweden	Riksmaten 2010	127	407	379	231	640	127	48	45	37	67
	United Kingdom	NDNS RollingProgramme Years 1–3	75	330	328	152	514	75	39	38.3	26	56
≥ 75 years	France	INCA2	40	285	279	(c)	(c)	40	37	35	(c)	(c)
	Ireland	NANS_2012	34	295	275	(c)	(c)	34	38	40	(c)	(c)
	Italy	INRAN_SCAI_2005_06	69	340	326	208	498	69	39	37	29	55
	Sweden	Riksmaten 2010	42	388	376	(c)	(c)	42	46	46	(c)	(c)
	United Kingdom	NDNS RollingProgramme Years 1–3	56	264	241	(c)	(c)	56	37	37	(c)	(c)

P5, 5th percentile; P95, 95th percentile; DIPP, Type 1 Diabetes Prediction and Prevention survey; DNFCS, Dutch National Food Consumption Survey; DNSIYC, Diet and Nutrition Survey of Infants and Young Children; EsKiMo, Ernährungsstudie als KIGGS-Modul; FINDIET, the national dietary survey of Finland; INCA, Étude Individuelle Nationale des Consommations Alimentaires; INRAN-SCAI, Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione – Studio sui Consumi Alimentari in Italia; FC_PREGNANTWOMEN, food consumption of pregnant women in Latvia; NANS, National Adult Nutrition Survey; NDNS, National Diet and Nutrition Survey; NWSSP, Nutrition and Wellbeing of Secondary School Pupils; VELs, Verzehrsstudie zur Ermittlung der Lebensmittelaufnahme von Säuglingen und Kleinkindern für die Abschätzung eines akuten Toxizitätsrisikos durch Rückstände von Pflanzenschutzmitteln.

(a): Number of individuals in the population group.

(b): The proportions of breast-fed infants were 58 % in the Finnish survey, 40 % in the German survey, 44 % in the Italian survey and 21 % in the UK survey. Most infants were partially breast-fed. For the Italian and German surveys, breast milk intake estimates were derived from the number of breastfeeding events recorded per day multiplied by standard breast milk amounts consumed on an eating occasion at different ages. For the UK survey, the amount of breast milk consumed was either directly quantified by the mother (expressed breast milk) or extrapolated from the duration of each breastfeeding event. As no information on the breastfeeding events was reported in the Finnish survey, breast milk intake was not taken into consideration in the intake estimates of Finnish infants.

(c): 5th or 95th percentile intakes calculated from fewer than 60 subjects require cautious interpretation, as the results may not be statistically robust (EFSA, 2011b) and, therefore, for these dietary surveys/age classes, the 5th and 95th percentile estimates will not be presented in the intake results.

Appendix D. Magnesium intake in females in different surveys according to age classes and country

Age	Country	Survey	n ^(a)	Intake expressed in mg/day				n ^(a)	Intake expressed in mg/MJ			
				Average	Median	P5	P95		Average	Median	P5	P95
< 1 year ^(b)	Finland	DIPP_2001_2009	252	72	73	14	132	251	45	43	27	81
	Germany	VELS	75	95	94	55	141	75	33	33	21	43
	Italy	INRAN_SCAI_2005_06	7	89	105	^(c)	^(c)	7	29	35	^(c)	^(c)
	United Kingdom	DNSIYC_2011	670	108	103	53	176	670	35	35	21	50
1 to < 3 years	Finland	DIPP_2001_2009	255	153	151	85	228	255	45	45	30	61
	Germany	VELS	174	155	149	93	234	174	36	35	26	51
	Italy	INRAN_SCAI_2005_06	16	166	168	^(c)	^(c)	16	35	34	^(c)	^(c)
	United Kingdom	DNSIYC_2011	651	156	152	87	242	651	40	39	27	54
	United Kingdom	NDNS RollingProgramme Years 1–3	78	174	167	99	278	78	38	38	26	51
3 to < 10 years	Finland	DIPP_2001_2009	369	226	222	150	311	369	43	42	33	55
	France	INCA2	243	199	197	128	286	243	36	34	26	51
	Germany	EsKiMo	409	259	251	158	386	409	38	38	27	50
	Germany	VELS	147	184	178	114	269	147	36	35	25	49
	Italy	INRAN_SCAI_2005_06	99	238	234	158	353	99	33	32	25	51
	Netherlands	DNFCS 2007–2010	216	225	217	138	341	216	28	28	18	40
	United Kingdom	NDNS RollingProgramme Years 1–3	325	218	211	128	328	325	36	35	26	51
10 to < 18 years	Finland	NWSSP07_08	170	292	285	166	443	170	44	44	31	60
	France	INCA2	524	213	207	122	321	524	34	33	24	48
	Germany	EsKiMo	196	278	275	172	395	196	37	37	27	48
	Italy	INRAN_SCAI_2005_06	139	261	251	161	397	139	33	32	23	51
	Latvia	FC_PREGNANTWOMEN_2011 ^(d)	12	384	394	^(c)	^(c)	12	39	40	^(c)	^(c)
	Netherlands	DNFCS 2007–2010	576	253	250	154	371	576	29	29	18	41
	United Kingdom	NDNS RollingProgramme Years 1–3	326	215	207	119	328	326	32	30	22	47
18 to < 65 years	Finland	FINDIET2012	710	334	322	192	503	710	47	45	31	67
	France	INCA2	1 340	254	245	141	403	1 340	40	38	27	59
	Ireland	NANS_2012	640	276	264	150	428	640	38	37	24	54
	Italy	INRAN_SCAI_2005_06	1 245	311	303	185	452	1 245	44	41	28	68
	Latvia	FC_PREGNANTWOMEN_2011 ^(d)	990	353	338	226	532	990	42	40	30	60
	Netherlands	DNFCS 2007–2010	1 034	302	290	174	469	1 034	37	36	23	57
	Sweden	Riksmaten 2010	807	357	335	193	604	807	51	45	30	72
	United Kingdom	NDNS RollingProgramme Years 1–3	706	258	252	133	406	706	39	37	25	58

Age	Country	Survey	n ^(a)	Intake expressed in mg/day				n ^(a)	Intake expressed in mg/MJ			
				Average	Median	P5	P95		Average	Median	P5	P95
65 to < 75 years	Finland	FINDIET2012	203	304	299	182	457	203	50	49	34	69
	France	INCA2	153	241	239	142	348	153	39	38	29	52
	Ireland	NANS_2012	77	297	287	162	445	77	44	43	27	60
	Italy	INRAN_SCAI_2005_06	157	298	293	181	434	157	44	42	30	65
	Netherlands	DNFCS 2007–2010	82	308	291	187	441	82	43	40	28	66
	Sweden	Riksmaten 2010	168	343	330	206	528	168	49	48	37	62
	United Kingdom	NDNS RollingProgramme Years 1–3	91	263	254	141	401	91	44	42	28	74
≥ 75 years	France	INCA2	44	232	232	(c)	(c)	44	39	37	(c)	(c)
	Ireland	NANS_2012	43	280	288	(c)	(c)	43	45	42	(c)	(c)
	Italy	INRAN_SCAI_2005_06	159	282	274	184	423	159	43	40	30	69
	Sweden	Riksmaten 2010	30	347	334	(c)	(c)	30	51	47	(c)	(c)
	United Kingdom	NDNS RollingProgramme Years 1–3	83	267	254	163	417	83	44	42	28	65

P5, 5th percentile; P95, 95th percentile; DIPP, Type 1 Diabetes Prediction and Prevention survey; DNFCS, Dutch National Food Consumption Survey; DNSIYC, Diet and Nutrition Survey of Infants and Young Children; EsKiMo, Ernährungsstudie als KIGGS-Modul; FINDIET, the national dietary survey of Finland; INCA, Étude Individuelle Nationale des Consommations Alimentaires; INRAN-SCAI, Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione – Studio sui Consumi Alimentari in Italia; FC_PREGNANTWOMEN, food consumption of pregnant women in Latvia; NANS, National Adult Nutrition Survey; NDNS, National Diet and Nutrition Survey; NWSSP, Nutrition and Wellbeing of Secondary School Pupils; VELs, Verzehrsstudie zur Ermittlung der Lebensmittelaufnahme von Säuglingen und Kleinkindern für die Abschätzung eines akuten Toxizitätsrisikos durch Rückstände von Pflanzenschutzmitteln.

(a): Number of individuals in the population group.

(b): The proportions of breast-fed infants were 58 % in the Finnish survey, 40 % in the German survey, 44 % in the Italian survey and 21 % in the UK survey. Most infants were partially breast-fed. For the Italian and German surveys, breast milk intake estimates were derived from the number of breastfeeding events recorded per day multiplied by standard breast milk amounts consumed on an eating occasion at different ages. For the UK survey, the amount of breast milk consumed was either directly quantified by the mother (expressed breast milk) or extrapolated from the duration of each breastfeeding event. As no information on the breastfeeding events was reported in the Finnish survey, breast milk intake was not taken into consideration in the intake estimates of Finnish infants.

(c): 5th or 95th percentile intakes calculated from fewer than 60 subjects require cautious interpretation, as the results may not be statistically robust (EFSA, 2011b) and, therefore, for these dietary surveys/age classes, the 5th and 95th percentile estimates will not be presented in the intake results.

(d): Pregnant women only.

Appendix E. Minimum and maximum percentage contribution of different food groups (FoodEx2 level 1) to magnesium intake in males

Food groups	Age						
	< 1 year	1 to < 3 years	3 to < 10 years	10 to < 18 years	18 to < 65 years	65 to < 75 years	≥ 75 years
Additives, flavours, baking and processing aids	< 0.1	< 0.1–0.1	0–0.2	0–0.3	0–0.1	0	0
Alcoholic beverages	< 0.1	< 0.1	< 0.1	< 0.1–1.7	3.7–10.5	3–8.5	2.8–6.8
Animal and vegetable fats and oils	< 0.1–0.3	< 0.1–0.4	0.1–0.6	0.1–0.6	0.1–0.5	0.1–0.5	0.1–0.5
Coffee, cocoa, tea and infusions	< 0.1–0.4	< 0.1–3.9	1.3–10.3	2–8.2	5.6–23.4	8–22.6	7.9–19.4
Composite dishes	0.1–3.5	0.3–5.9	0.1–5.9	0.3–8.6	0.5–8.3	0.6–7.6	0.4–7.6
Eggs and egg products	< 0.1–0.2	0.2–0.6	0.2–0.9	0.2–0.9	0.2–0.9	0.2–0.9	0.3–0.8
Fish, seafood, amphibians, reptiles and invertebrates	< 0.1–0.4	0.2–3.1	0.3–3.1	0.3–3	0.7–2.7	0.9–3.7	2.2–4.1
Food products for young population	20.6–46.1	2.6–11	0.2–0.7	< 0.1–0.1	< 0.1	–	–
Fruit and fruit products	3.4–14.3	8.9–10.2	3.8–6.8	2.7–4.9	2.6–5.2	3.9–7.6	4.8–7
Fruit and vegetable juices and nectars	0.3–1.7	0.8–3.9	2.1–5.7	1.9–5.3	0.7–3.3	0.3–2.6	0.5–2.1
Grains and grain-based products	4.6–19	24–29.9	22.8–39.5	26.5–40.8	21.8–33.6	21.2–36.9	21.5–39.9
Human milk	< 0.1–16.1	< 0.1–0.6	–	–	–	–	–
Legumes, nuts, oilseeds and spices	0.7–2.4	1.4–3.8	1.6–5.6	2–5.1	2.3–5.7	2.4–6.5	1.6–3.8
Meat and meat products	0.4–3.8	3.1–6.5	4.8–9.1	5.6–11.2	5.9–11	5.7–10.1	5–9.3
Milk and dairy products	8.5–15.5	21.5–27.6	14.7–30.1	11.2–25.3	7.4–15.1	6.7–14.4	9.3–12
Products for non-standard diets, food imitates and food supplements or fortifying agents	0.1–0.6	0–0.6	< 0.1–1	0.1–0.8	< 0.1–2.2	< 0.1–0.5	< 0.1–1.5
Seasoning, sauces and condiments	0.1–0.4	0.6–2.4	0.2–2.1	0.2–2.3	0.2–2.2	0.2–2.3	0.2–2.6
Starchy roots or tubers and products thereof, sugar plants	0.6–11.9	2.9–10.4	4.4–9.1	5.3–11	3.6–9.7	3.7–11.1	4.8–10.7
Sugar, confectionery and water-based sweet desserts	< 0.1–0.3	0.2–4.1	2.1–5.7	2.3–6	0.8–2.4	0.3–1.8	0.3–2.1
Vegetables and vegetable products	1.1–8.7	2.5–5.9	3–8.4	2.9–10.7	2.2–11.2	2.4–12.6	2.9–10.7
Water and water-based beverages	1.3–17.5	2.5–6.9	1.9–7	2.6–7.9	1.8–6.2	1.2–5.6	1.2–5.9

“–” means that there was no consumption event of the food group for the age and sex group considered, while “0” means that there were some consumption events, but that the food group does not contribute to magnesium intake in the age and sex group considered.

Appendix F. Minimum and maximum percentage contribution of different food groups (FoodEx2 level 1) to magnesium intake in females

Food groups	Age						
	< 1 year	1 to < 3 years	3 to < 10 years	10 to < 18 years	18 to < 65 years	65 to < 75 years	≥ 75 years
Additives, flavours, baking and processing aids	< 0.1	0–0.1	0–0.2	0–0.2	0–0.1	0	0
Alcoholic beverages	< 0.1	< 0.1	< 0.1	< 0.1–0.3	< 0.1–3.9	0.6–3.3	1.2–1.9
Animal and vegetable fats and oils	< 0.1–0.3	0.1–0.4	0.1–0.6	0.1–0.6	0.1–0.5	0.1–0.5	0.1–0.5
Coffee, cocoa, tea and infusions	< 0.1–0.4	0.1–5	0.4–11.2	2.7–8.2	5.3–23.4	11.5–22.1	9.9–22
Composite dishes	< 0.1–1.9	0.3–5.7	0.1–5.9	0.4–9	0.5–8.6	0.3–9.1	0.5–7.8
Eggs and egg products	< 0.1–0.2	0.2–0.6	0.3–1.3	0.1–1	0.3–0.8	0.3–0.8	0.3–0.9
Fish, seafood, amphibians, reptiles and invertebrates	0–0.4	0.1–3.5	0.2–2.5	0.3–4	0.7–2.8	0.8–3.7	1.7–3.4
Food products for young population	20.1–51.9	2.3–11.1	< 0.1–0.4	< 0.1–0.1	< 0.1	–	< 0.1
Fruit and fruit products	7.5–12.7	6.4–9.5	4.1–7.4	3.5–10.4	4.1–7.6	5.8–9.5	5.8–9.3
Fruit and vegetable juices and nectars	0.1–1.3	0.8–3.8	2.1–5.1	1.8–5.3	0.8–2.8	0.8–2.3	0.8–2.1
Grains and grain-based products	12.9–18.9	23.4–34	21.7–38.6	25.6–38.9	20.2–35.4	18.9–35.5	17–38.5
Human milk	< 0.1–6.8	< 0.1–0.5	–	–	–	–	–
Legumes, nuts, oilseeds and spices	0.6–3	1.3–4.1	1.9–4.7	2.2–4.5	2.5–6.5	2.5–5.1	2.2–4.9
Meat and meat products	0.7–3.2	3.1–5.3	4.3–9.5	5.3–10.1	5.3–9	4.4–8.8	4–8.4
Milk and dairy products	4.6–21.8	20.4–31.2	14.7–30.3	10.1–22	8.5–15.7	8.4–14.5	10.2–13.1
Products for non-standard diets, food imitates and food supplements or fortifying agents	< 0.1–0.4	< 0.1–0.6	0–1.3	< 0.1–1	0.1–3.8	0.2–0.9	< 0.1–1.8
Seasoning, sauces and condiments	0.2–0.5	0.2–0.8	0.4–2.1	0.1–2.4	0.2–2.4	0.2–3.1	0.3–2.9
Starchy roots or tubers and products thereof, sugar plants	2.4–11.5	4.8–9.1	4.9–9.8	5–11	3.5–9.9	4.2–8.3	4–7.6
Sugar, confectionery and water-based sweet desserts	< 0.1–1.2	0.2–3.7	2.1–6.2	2.6–6.1	0.8–7.6	0.4–2	0.4–2.3
Vegetables and vegetable products	3.3–9.4	2.2–6.6	3.3–8.5	3.4–11	3.4–12.1	3.3–13.1	3.9–12.7
Water and water-based beverages	1.5–10.8	2.5–7.7	1.9–7	1.6–7.9	1.3–7.5	1.7–7	1.7–7.5

“–” means that there was no consumption event of the food group for the age and sex group considered, while “0” means that there were some consumption events, but that the food group does not contribute to magnesium intake in the age and sex group considered.

Appendix G. Balance studies in adults with adaptation periods of ≥ 12 days

Reference	Number of subjects	Characteristics	Experimental period	Data collection for balance	Magnesium intake (mg/day unless otherwise indicated), mean \pm standard error	Balance (mg/day), mean \pm standard error	Comments
Andersson et al. (1983)	6 subjects, 1 woman, 5 men	25–55 years	Three consecutive 24-day periods, 12 days of adaptation	Daily collection during final 12 days of each dietary period, urine and faecal losses considered	A: $236 \pm 29/224 \pm 29^{(a, b)}$ B: $309 \pm 19/309 \pm 19^{(a, b)}$ C: $403 \pm 19/403 \pm 19^{(a, b)}$ Duplicate diet analysis	A: $-9.7 \pm 26.7/-19.4 \pm 19.4^{(a, b)}$ B: $-34.0 \pm 19.4/-26.7 \pm 26.7^{(a, b)}$ C: $-19.4 \pm 24.3/-14.6 \pm 12.2^{(a, b)}$	Subjects housed in a metabolic ward; periods differed by the type of bread providing 3.3 (A), 10.9 (B) or 18.7 g (C) of non-starch polysaccharides/day and about 2.1–2.3 mmol phytate/day, mean total fibre intake 16.1 (A), 23.7 (B) or 31.5 (C) g/day
Hunt and Johnson (2006)	150 women, 93 men	Women: 19–77 years Men: 19–65 years	At least 18 days including balance, and at least 12 days of adaptation (median 31 days)	Final 6–14 days, urine and faecal losses considered	Intake 84–598, including supplemental magnesium in some studies Duplicate diet analysis	165 mg/day (null balance)	Pooled analysis of 27 studies (664 data points) carried out from 1976 to 2001 in a metabolic ward under strict supervision of subjects; studies with supplements used Mg gluconate in addition to the diet, except for one study that used Mg citrate dibasic Fibre intake \approx 3.5–20 g/day

Reference	Number of subjects	Characteristics	Experimental period	Data collection for balance	Magnesium intake (mg/day unless otherwise indicated), mean \pm standard error	Balance (mg/day), mean \pm standard error	Comments
Kelsay and Prather (1983)	12 men	34–58 years, 61–97 kg	4 weeks	During weeks 3 and 4, urine and faecal losses considered	A: $300 \pm 11/308 \pm 10^{(b)}$ B: $375 \pm 10/350 \pm 7^{(b)}$ C: $346 \pm 10/326 \pm 10^{(b)}$ Duplicate diet analysis	A: $-20 \pm 14/20 \pm 14^{(b)}$ B: $28 \pm 10/-10 \pm 13^{(b)}$ C: $21 \pm 5/18 \pm 13^{(b)}$	Subjects housed in a metabolic ward during the week, but no supervision on weekends; diets were low fibre with spinach (A), higher fibre with spinach (B) and higher fibre without spinach (C); when pooling data for weeks 3 and 4, diet had no effect on magnesium balance
Kelsay et al. (1979)	12 men	37–58 years	26 days	Last 7 days, urine and faecal losses considered	356 ± 10 (low-fibre diet) 322 ± 12 (high-fibre diet) Duplicate diet analysis	28 ± 17 (low-fibre diet) -32 ± 10 (high-fibre diet)	Sources of fibre in the high-fibre diet were fruits and vegetables
Lakshmanan et al. (1984)	18 women, 16 men	20–53 years	1 year	1 week per season, four collection periods in total, urine and faecal losses considered	234 (women), 323 (men), 0.14 mg/kcal per day (both sexes), 4.3 mg/kg body weight per day (men) 4.15 mg/kg body weight per day (women) Duplicate diet analysis	-25 mg/day (women) -32 mg/day (men)	Self-selected diets, free-living subjects Effect of magnesium, calcium, phosphorus, protein and fibre intakes on urinary and faecal excretion and balance tested separately in men and women, with no consistent influence noted
Mahalko et al. (1983)	10 men	19–64 years, 76 ± 11 kg ^(a)	28 days, 16 days of adaptation	Last 12 days, urine and faecal losses considered	$229 \pm 24^{(a)}$ $258 \pm 24^{(a)}$ Duplicate diet analysis	13 ± 30 (65 g protein/day) ^(a) 17 ± 36 (94 g protein/day) ^(a)	Subjects housed in a metabolic ward; the study was done at USDA but not included in the pooled analysis of Hunt and Johnson (2006)

Reference	Number of subjects	Characteristics	Experimental period	Data collection for balance	Magnesium intake (mg/day unless otherwise indicated), mean \pm standard error	Balance (mg/day), mean \pm standard error	Comments
Nielsen and Milne (2004)	21 post-menopausal women	50–76 years, 65.1 \pm 9.5 kg ^(a)	2 dietary periods of 90 days each, 12 days of adaptation	Last 78 days, urine and faecal losses considered	328 (low Cu, low Zn) 313 (low Cu, high Zn) 334 (high Cu, low Zn) 310 (high Cu, high Zn), 180 mg/day as supplemental Mg gluconate Duplicate diet analysis	23.1 (low Cu, low Zn) 1.0 (low Cu, high Zn) 26.0 (high Cu, low Zn) 5.6 (high Cu, high Zn)	Subjects housed in a metabolic ward, four diets combining high (3 mg) and low (1 mg) copper with high (53 mg) and low (3 mg) zinc intakes daily, high dietary zinc significantly decreased magnesium balance. The study was done at USDA but not included in the pooled analysis of Hunt and Johnson (2006)
Schwartz et al. (1986)	7 men	22–32 years	49 days in total, of which 21 days of adaptation	Complete faecal and urine collections were made from day 8	657 \pm 85 (weeks 2-4) 719 \pm 105 (weeks 5-7) Duplicate diet analysis	-25 \pm 16 ^(a) (weeks 2-4) 27 \pm 19 ^(a) (weeks 5-7)	The objective was to determine apparent magnesium absorption in the presence of bran
Schwartz et al. (1984)	8 men	48–62 years, 55–94 kg	100–130 days, at least 30 days of adaptation	Collection of urine and faeces throughout the study	331–447 (range for the subjects throughout the study)	6–48 (range)	Subjects housed in a metabolic ward, study focused on magnesium absorption from four freeze-dried leafy vegetables incorporated into muffins
Schwartz et al. (1978)	4 men	48–75 years, 67–83 kg	146 days, at least 35 days of adaptation	Days 66–76 and 109–119, urine and faecal losses considered	243–321, including 50 mg/day of supplemental Mg oxide	Individual balances from –44 to +20 (4 positive or null, 4 negative)	Subjects housed in a metabolic ward, objective of the study was magnesium absorption

Reference	Number of subjects	Characteristics	Experimental period	Data collection for balance	Magnesium intake (mg/day unless otherwise indicated), mean \pm standard error	Balance (mg/day), mean \pm standard error	Comments
Spencer et al. (1994)	5 men	38–75 years	Unclear, but at least 28 days of adaptation	Unclear if more than 6 days, urine and faecal losses considered	240 \pm 24 (normal Ca) 264 \pm 26 (low Ca) Duplicate diet analysis; periods with supplemental Mg not considered here	–26 \pm 14 (normal Ca, 800 mg/day) –23 \pm 21 (low Ca, 240 mg/day)	Subjects housed in a metabolic ward
van Dokkum et al. (1983)	10–12 men (10 in study A and 12 in study B)	23 \pm 2 years ^(a) , 67 \pm 6 kg ^(a)	2 dietary periods of 20 days each, preceded by adaptation periods of 8–16 days	20 days of each dietary period. Urine and faecal losses considered.	Study A: 389 \pm 34 (high fat diet) ^(a) 367 \pm 25 (low fat diet) ^(a) Study B: 312 \pm 24 (low linoleic acid diet) ^(a) 319 \pm 26 (high linoleic acid diet) ^(a) Duplicate diet analysis	16 \pm 23 (high fat diet) ^(a) 3 \pm 15 (low fat diet) ^(a) 10 \pm 15 (low linoleic acid diet) ^(a) 7 \pm 13 (high linoleic acid diet) ^(a)	The objective was to determine the influence of fat and linoleic acid on absorption and balance
Wisker et al. (1991)	12 women	22–28 years	Three separate experiments each for 22 days	Last 6 days (from days 16 to 22), urine and faecal losses considered	252 \pm 9 245 \pm 8 243 \pm 9 Duplicate diet analysis	7.3 \pm 4.9 4.9 \pm 2.4 –12 \pm 4.9	Comparison of low fibre (22.5 g/day and 1.1 g protein/kg body weight per day), high fibre/high protein (38.6 g/day and 1.1 g protein/kg body weight per day) and high fibre/adequate protein (38.6 g/day and 0.8 g protein/kg body weight per day)

USDA, US Department of Agriculture. Studies not included in this table because of adaptation periods of fewer than 12 days: Slavin and Marlett (1980); Greger and Baier (1983); Nishimuta et al. (2006); Nishimuta et al. (2012) and McDonald and Margen (1979). Study not included in this table because of short duration of adaptation and balance periods: Jones et al. (1967).

(a): Mean value \pm SD.

(b): Values for 3rd/4th period of 6 or 7 days.

Appendix H. Balance studies in children

Reference	Number of subjects	Age (years), mean \pm standard deviation	Experimental period	Data collection for balance	Magnesium intake (mg/day unless otherwise specified), mean \pm standard deviation	Balance (mg/day unless otherwise specified), mean \pm standard deviation	Comments
Abrams et al. (1997)	12 boys 13 girls	10.9 \pm 1.1 12.3 \pm 1.6	10 days	Mg absorption studied using tracers. Balance calculated as the difference between dietary absorption and the sum of endogenous faecal and urinary excretion (means of the first 7 days of the study)	261 \pm 40 (6.4 \pm 1.2 mg/kg per day) (range 194–321)	15.6 \pm 36.8 (boys) –0.9 \pm 41.2 (girls)	11 out of 25 subjects were in negative balance
Andon et al. (1996)	13 girls 13 girls	11.3 \pm 0.5 11.3 \pm 0.7	14 days	First week of the study was considered as adaptation period. Samples from the 2 nd week used to calculate magnesium balance	Basal diet: 193 \pm 39 Basal diet plus Ca supplement: 199 \pm 45	19 \pm 25 (basal diet) 22 \pm 15 (basal diet plus Ca supplement)	Balance was positive in all subjects with a magnesium intake > 5 mg/kg per day. Calcium intake had no effect on magnesium balance
Greger et al. (1978)	14 girls	12.5–14.5 (range)	30 days in total. 9 days adaptation, 21 days for experimental diets	Meal and urine samples on a daily basis, faecal samples pooled for 6-day periods. Excreta not collected during the first 3 days of adaptation and experimental periods	Adaptation: 196 \pm 17 $S_0Z_{13.4}$: 190 \pm 26 $S_{30}Z_{7.4}$: 195 \pm 29 $S_{30}Z_{13.4}$: 195 \pm 29	–5.0 \pm 26.8 (adaptation) –5.6 \pm 16.5 ($S_0Z_{13.4}$) –6.8 \pm 10.4 ($S_{30}Z_{7.4}$) –1.8 \pm 2.2 ($S_{30}Z_{13.4}$)	Magnesium intake via the metabolic diet was insufficient for most of the girls to maintain positive balances

Reference	Number of subjects	Age (years), mean \pm standard deviation	Experimental period	Data collection for balance	Magnesium intake (mg/day unless otherwise specified), mean \pm standard deviation	Balance (mg/day unless otherwise specified), mean \pm standard deviation	Comments
Schofield and Morrell (1960)	35 girls	7–9	7 weeks	Not reported	From 135.6 ± 2.5 to 231.7 ± 12.7 in three different groups	All balances positive (from 10.4 ± 6.4 to 16.2 ± 8.6)	Positive balances were maintained on low protein diets (17–20 g/day)
Schwartz et al. (1973)	12 boys	13–14	Two 30-day periods (in subsequent years) with a constant protein intake, whereas Mg intake level changed after 15 days of each experimental period	10 days. First 5 days of each 15-day dietary period regarded as adaptation period and excreta not collected	LPLM: $4.3 \pm 0.21^{(a)}$ LPHM: $14.5 \pm 0.61^{(a)}$ HPLM: $4.1 \pm 0.16^{(a)}$ HPPM: $13.1 \pm 0.51^{(a)}$	-0.62 ± 0.07 (LPLM) ^(a) 0.88 ± 0.48 (LPHM) ^(a) 0.19 ± 0.08 (HPLM) ^(a) 1.25 ± 0.26 (HPPM) ^(a)	Diets with either low or high amounts of protein (43 g/day or 93 g/day) or magnesium. Magnesium retention was significantly increased by consumption of the high-protein diet
Sojka et al. (1997)	5 girls	12–14	Two 21-day periods with 5-week intervals in between, with the first 7 days considered as adaptation	Blood, urine and faecal samples were collected during last 14 days	800 mg Ca (control): 305 ± 30 1 800 mg Ca (high Ca diet): 286 ± 9	13 ± 35 (control, 1 of 5 negative) -34 ± 48 (high Ca diet, 4 of 5 negative)	

Ca, calcium; S₀,Z_{13.4}, 13.4 mg zinc and no soy; S₃₀,Z_{13.4}, 13.4 mg zinc and 30 % of meat replaced by soy; S₃₀,Z_{7.4}, 7.4 mg zinc and 30 % of meat replaced by soy; LPLM, low-protein, low-magnesium diet; LPHM, low-protein, high-magnesium diet; HPLM, high-protein, low-magnesium diet; HPPM, high-protein, high-magnesium diet

(a): mg/kg per day.

Appendix I. Characteristics of prospective cohort studies on magnesium intake and risk of diabetes mellitus type 2 (adapted from Dong et al. (2011))

Reference	Number of subjects, place of study (number of cases)	Age (years)	Duration (years)	Median magnesium intake (highest vs. lowest, mg/day)	Adjusted RR unless otherwise specified (95 % CI)	Adjustment for potential confounders
Hodge et al. (2004)	31 641 adults, Australia (365)	40–69	4	773 vs. 230 ^(a)	0.55 (0.32–0.97)	Age, BMI, sex, education, country of birth, family history, WHR, weight change, physical activity, and intakes of total energy and alcohol
Hopping et al. (2010)	75 512 adults, USA (8 587)	45–75	14	370 vs. 260 ^(b)	Men: 0.77 (0.70–0.85) Women: 0.84 (0.76–0.93)	BMI, physical activity, education, ethnicity and total energy intake
Kao et al. (1999)	11 896 adults, USA (1 106)	45–64	6	361 vs. 154 ^(c)	White: 1.08 (0.78–1.49) Black: 0.98 (0.57–1.72)	Age, BMI, sex, education, family history, WHR, sports index, diuretic use, and intakes of alcohol, calcium and potassium
Kim et al. (2010)	4 497 adults, USA (330)	18–30	20	403 vs. 200 ^(d)	0.53 (0.32–0.86)	Age, BMI, sex, ethnicity, study centre, education, smoking, physical activity, family history, systolic blood pressure, and intakes of total energy, alcohol, saturated fat and crude fibre
Kirii et al. (2010)	17 592 adults, Japan (459)	40–65	5	303 vs. 158	0.64 (0.44–0.94)	Age, BMI, family history, smoking, hours of walking and sports participation, and intakes of total energy, alcohol, green tea and coffee
Lopez-Ridaura et al. (2004)	42 872 men, USA (1 333)	40–75	11	457 vs. 270	0.72 (0.58–0.89)	Age, BMI, family history, hypertension, hypercholesterolaemia, smoking, physical activity, and intakes of total energy, alcohol, glycaemic load, PUFA, TFA, processed meat and cereal fibre
Lopez-Ridaura et al. (2004)	85 060 women, USA (4 085)	30–55	17	374 vs. 222	0.73 (0.65–0.82)	Age, BMI, family history, hypertension, hypercholesterolaemia, smoking, physical activity, and intakes of total energy, alcohol, glycaemic load, PUFA, TFA, processed meat and cereal fibre
Meyer et al. (2000)	35 988, USA (1 141)	55–69	6	362 vs. 220	0.67 (0.55–0.82)	Age, BMI, education, smoking, WHR, physical activity, intakes of total energy, alcohol, whole grains and cereal fibre

Reference	Number of subjects, place of study (number of cases)	Age (years)	Duration (years)	Median magnesium intake (highest vs. lowest, mg/day)	Adjusted RR unless otherwise specified (95 % CI)	Adjustment for potential confounders
Nanri et al. (2010)	59 791 adults, Japan (1 114)	45–75	5	348 vs. 213	Men: 0.86 (0.63–1.16) Women: 0.92 (0.66–1.28)	Age, BMI, study area, smoking, family history, leisure time physical activity, hypertension, and intakes of total energy, alcohol, coffee and calcium
Schulze et al. (2007)	25 067 adults, Germany (844)	35–65	7	377 vs. 268	0.99 (0.78–1.26)	Age, BMI, sex, education, sports activity, cycling, occupational activity, smoking, WC, and intakes of total energy, alcohol, carbohydrate, PUFA to SFA ratio, MUFA to SFA ratio and cereal fibre
Song et al. (2004)	38 025 women, USA (918)	≥ 45	6	399 vs. 252	0.89 (0.71–1.10)	Age, BMI, family history, smoking, physical activity, and intakes of total energy and alcohol
van Dam et al. (2006)	41 186 women, USA (1 964)	21–69	6	244 vs. 115	0.65 (0.54–0.78)	Age, BMI, education, family history, smoking, physical activity, and intakes of total energy, alcohol, coffee, sugar-sweetened drinks, red meat, processed meat and calcium
Villegas et al. (2009)	64 191 women, China (2 270)	40–70	6.9	318 vs. 214	0.80 (0.68–0.93)	Age, BMI, WHR, smoking, physical activity, income, education, occupation, hypertension, and intakes of total energy and alcohol
Weng et al. (2012)	1 604 adults, Taiwan (141)	38–63	4.6	406 vs. 212	2.61 (1.42–4.79) ^(e)	Age, sex, age–sex interaction, caloric intake, residential area, family history of diabetes, BMI, central obesity, education, smoking habits, current drinking habits, frequency of activity, hypertension, hypercholesterolaemia, hypertriglyceridaemia and low high-density lipoprotein cholesterol

BMI, body mass index; CI, confidence interval; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; RR, relative risk; SFA, saturated fatty acid; TFA, trans fatty acid; WC, waist circumference; WHR, waist to hip ratio.

(a): The primary paper reports median magnesium intake (g/day) across glycaemic index quartiles.

(b): The primary paper reports median magnesium intake expressed as g/4 184 kJ per day.

(c): The primary paper reports mean magnesium intake expressed as mg/4.2 kJ per day.

(d): The primary paper reports median magnesium intake expressed as mg/1 000 kcal per day.

(e): Hazard ratio using the highest quintile as the reference category.

ABBREVIATIONS

Afssa	Agence française de sécurité sanitaire des aliments
AI	Adequate Intake
AR	Average Requirement
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
CI	confidence interval
COMA	Committee on Medical Aspects of Food Policy
CV	coefficient of variation
CVD	cardiovascular disease
Da	dalton
D-A-CH	Deutschland–Austria–Confoederatio Helvetica
DBP	diastolic blood pressure
DH	UK Department of Health
DIPP	Type 1 Diabetes Prediction and Prevention
DNFCS	Dutch National Food Consumption Survey
DNSIYC	Diet and Nutrition Survey of Infants and Young Children
DRV	Dietary Reference Value
EAR	Estimated Average Requirement
EsKiMo	Ernährungsstudie als KIGGS-Modul
EU	European Union
FAO	Food and Agriculture Organization
FINDIET	National dietary survey of Finland
INCA	Étude Individuelle Nationale des Consommations Alimentaires
INRAN-SCAI	Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione – Studio sui Consumi Alimentari in Italia
IOM	US Institute of Medicine of the National Academy of Sciences

NANS	National Adult Nutrition Survey
NDNS	National Diet and Nutrition Survey
NNR	Nordic Nutrition Recommendations
NOAEL	No Observed Adverse Effect Level
NWSSP	Nutrition and Wellbeing of Secondary School Pupils
PRI	Population Reference Intake
RI	Recommended Intake
RDA	Recommended Dietary Allowance
RR	relative risk
SBP	systolic blood pressure
SCF	Scientific Committee for Food
UL	Tolerable Upper Intake Level
VELS	Verzehrsstudie zur Ermittlung der Lebensmittelaufnahme von Säuglingen und Kleinkindern für die Abschätzung eines akuten Toxizitätsrisikos durch Rückstände von Pflanzenschutzmitteln
WHO	World Health Organization